Should We Really Compare Indwelling Pleural Catheters to Any Pleurodesis?

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Pleural effusion is a common manifestation of malignancies, which either reveals the disease or occurs during the course of the disease. Overall, 150,000 new cases of malignant pleural effusions (MPE) are reported every year in the USA. Any neoplasm may lead to this manifestation: in primary tumors of the pleura (mesothelioma), it occurs in up to 95% of the cases, whereas in metastatic neoplasms in males lung carcinomas account for 40% and in females breast carcinomas account for 30% [1, 2]. Although the survival of patients with MPE is globally reported to be poor, we have to differentiate between patients with MPE as an initial manifestation of the disease, who are naïve to any treatment, and patients with MPE occurring during disease progression, who are relapsing and/or resisting to treatment [3].

Pleurodesis is a process involving multiple inflammatory cells recruited by cytokines, which leads to a coagulation-fibrinolysis imbalance and finally a development of adhesions between visceral and parietal pleurae in order to obliterate the pleural space to palliate effusion and symptoms [4]. Relief of dyspnea may be obtained regardless of radiographic findings. For pleurodesis, many compounds have been tested. The cheapest compound providing long-lasting pleurodesis is sterile, asbestos-free, calibrated Luzenac talc [5]. Talc insufflation, after evacu-

ation of the fluid and adhesiolysis during thoracoscopy, showed excellent immediate (>90%) and 1-year (85%) results [6], with few side effects, producing better quality and quantity of pleural symphysis compared to talc slurry [7]. Talc seems to have another interesting local antitumor effect, the induction of apoptosis of cancer cells [4, 8]. Iodopovidone is an interesting alternative to talc for pleurodesis as it is cheap, safe and showed high efficacy rates (90%) [9]. Many chemotherapeutic agents, such as bleomycin, cisplatin and taxanes, which have lower efficacy but at the same time highest costs, have been tested [10]. New molecules such as cytokines (transforming growth factor- β), which are involved in the coagulation cascade [11], are expensive, and data in humans are still lacking. To date, thoracoscopy with Luzenac talc pouddrage remains the most effective low-cost method of pleurodesis in patients with MPE, a good performance status and long life expectancy [12–14].

Studies reporting data from patients with recurrent non-MPE are mainly retrospective or include only a small number of patients with many different causes of their disease (inhomogeneous population) [15–17]. Frequently, benign diseases necessitating an intervention in case of refractory pleural effusion are congestive heart failure, renal failure and hepatic cirrhosis [15, 16]. Patients with

these diseases consult physicians repeatedly over a short period of time in order to palliate dyspnea, the leading symptom, which is, however, not only caused by the presence of effusion. They do not respond to diuretic therapy or develop diuretic-related complications that prevent the use of high doses of these drugs [16]. In these patients, many interventions, such as repeated thoracentesis, pleurodesis, pleuroperitoneal, transjugular intrahepatic portosystemic shunts or repair of the defects of the diaphragm, may be considered depending on the underlying disease and the patients' health status. In these cases, pleurodesis performed with talc (poudrage or slurry) or autologous blood proved neither efficient nor long-lasting. Interventions such as pleuroperitoneal shunts, transjugular intrahepatic portosystemic shunts or diaphragmatic defect repair are invasive, costly procedures which need to be dealt with by experienced teams [16, 18]. In practice, many of these patients are subjected to frequent and repeated therapeutic thoracenteses in order to drain as much fluid as possible from their pleura for symptom relief.

In the last decade, indwelling pleural catheters (IPCs) have been developed and studied mainly in MPE patients (see Bhatnagar and Maskell [19] in this issue of *Respiration*). The primary goal of treatment is the relief of dyspnea rather than pleurodesis, yet 'spontaneous pleurodesis' occurs in a subset of patients (about 40%) allowing secondary catheter removal [20]. Initial clinical assessment and follow-up by a respiratory physician are mandatory [19, 20]. Catheters are inserted in the endoscopy suite or in an outpatient setting under local anesthesia similar to any classic small-bore chest tube. Symptom relief is achieved rapidly following its placement, and the relief of dyspnea is maintained along with eventual lung expansion by repeated drainage through the catheter in an outpatient setting. Drainage is performed every other day using disposable plastic bottles (0.5–1 liters), while patients with rapid fluid re-accumulation require daily procedures. Home care nursing support for catheter care and drainage is mandatory [20]. Patients and family members are also encouraged to learn the drainage procedure, facilitating additional drainage if necessary [20]. Although costs seem to be acceptable [21], they need to cover all treatments, interventions (including those at home) and materials related to the care of IPC-treated patients. In a recent study [22], repeat thoracentesis was the cheapest intervention (USD 4,946) in the 3-month survival analysis while bedside pleurodesis was the cheapest in the 12-month analysis (USD 13,057). Unfortunately, to this day, there are no prospective long-term data

directly comparing the costs of different methods; therefore, more research is needed in this area [20]. However, should we really compare IPC to pleurodesis?

In patients with malignant pleurisy, a study comparing IPCs to talc pleurodesis showed significantly shorter hospital stays, successful relief of dyspnea for IPCs and no difference in the complication rates [23]. However, it is important to notice that in this study the pleurodesis arm was inhomogeneous as patients treated with talc slurry and medical and surgical thoracoscopy poudrage were included. When adjusted for follow-up modalities, there was no significant improvement in duration of hospitalization or relief of dyspnea [23]. A more recent study randomizing IPCs to talc slurry showed an equal relief of dyspnea and quality of life with a shorter hospital stay, while overall complications rates were significantly higher (40 vs. 13%) for the group treated with IPCs [24]. Furthermore, a newer technique, although preliminary, combining thoracoscopy poudrage with IPC suggests that pleurodesis is feasible and allows patients to be discharged the day after the procedure [25].

Complications are different from one method to another and therefore difficult to compare [20]. The most frequent IPC complications are dislocation of the catheter, local infections, repositioning of the catheter due to initial misplacement, pain and discomfort of the patient related to the long-term port access and catheter blockage leading to poor drainage and finally catheter removal [19]. These complications may be related to changes in IPC materials produced, which necessitate a close surveillance protocol [26]. Complications of pleurodesis are mainly subcutaneous emphysema, local infections, and pain during and after the procedure. A slight increase in body temperature due to local inflammatory reactions producing symphysis should not be considered as a complication [27]. Respiratory failure and acute respiratory distress syndrome (ARDS) as a result of talc does not concern Luzenac talc, and it is a huge mistake not to differentiate between different kinds of talc [12, 13]. Indeed, a previous study in animals clearly showed no systemic dissemination or organ deposition of Luzenac talc particles [28]. These data were confirmed by a large clinical trial, which did not show a single case of ARDS [29]. Small-particle talc is associated with ARDS, respiratory insufficiency and poor outcome of pleurodesis [30], and, therefore, it should not be used any longer [12, 13]. Mortality rates related to the procedure are extremely low for both IPCs [19, 20] and pleurodesis [14, 31]. In case of thoroscopic talc pleurodesis, mortality is related to the patient's general

health status and underlying respiratory condition [32] affecting respiratory muscle strength [33], while it is related to local complications in case of IPCs [20].

Also, techniques are different and therefore patient selection is different for pleurodesis or IPC. IPC introduction is a minimally invasive technique, which is performed in a sterile environment in patients with sufficient cytological confirmation with the simple goal of dyspnea relief. Thoracoscopy performed in the endoscopy suite is more invasive since it is also performed to obtain biopsies necessary for a histological diagnosis. When there is evidence of malignant lesions or when a rapid on-site diagnosis is available, the operator performs talc poudrage in the same setting after the evacuation of the fluid and adhesiolysis [34].

Thoracoscopic pleurodesis as first-line treatment is reserved for patients with a good health status and a long life expectancy, in whom a histological diagnosis is important together with anatomic and molecular staging of

the disease, leading to changes in the treatment strategy [35–37]. IPCs should be utilized as second-line treatment after the failure of pleurodesis in MPE patients with adhesions or trapped lung, and in patients deemed unsuitable to undergo thoracoscopy due to a poor performance status and a short life expectancy, in the same way as bedside pleurodesis through a chest tube is indicated with different compounds. On the other hand, in case of non-MPE, IPC seems to be an interesting first-line treatment [38] either for elderly patients with end-stage disease or for young patients waiting for a heart, kidney or liver transplantation, in view of the fact that pleurodesis failed to achieve high efficacy in controlling dyspnea.

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The author has no conflicts of interest to disclose.

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