Pleurodesis for recurrent malignant pleural effusions: the quest for the Holy Grail

Keywords: Pleurodesis; Pleural cancer; Talc; Pleural symphysis; Pleural effusions

Recurrent and symptomatic pleural effusions are common in patients with malignancy. Up to 25% of patients with lung cancer and 50% of patients with breast cancer will develop a pleural effusion. Overall, mesothelioma, and breast and lung cancer, account for the majority of malignant pleural effusions [1]. A minority of effusions remain asymptomatic and few cancers involving the pleura can be cured by specific antineoplastic or hormonal treatment. Therefore, the majority of patients will need a procedure to remove the fluid and prevent recurrence.

As a first step, a therapeutic thoracocentesis should be performed. This usually leads to symptomatic relief and rules out trapped lung. However, pleurodesis is considered the best palliative therapy for the treatment of recurrent malignant pleural effusions [2]. Several techniques and various agents have been used for this purpose, with variable efficacy and safety. The search for the ideal agent and the optimal mode of administration still remains the Holy Grail. An ideal agent for pleural symphysis should be inexpensive, efficient, and safe. It is surprising that many authors have attempted to discredit talc despite evidence from relevant prospective publications. In the prospective phase III intergroup study performed by Dresler and colleagues, 501 registered patients with recurrent malignant pleural effusions were randomized to thoracoscopic talc poudrage or talc slurry (TS). The primary end point was the 30-day freedom from radiographic recurrence of malignant pleural effusion in patients whose lungs initially re-expanded >90% [3]. Morbidity, mortality, and quality of life were also assessed. There was no difference between the study arms regarding the percentage of patients with successful 30-day outcomes. Patients with lung or breast cancer had statistically significant higher success rates with thoracoscopic talc poudrage compared with TS. In addition, the incidence of respiratory complications occurring during this study brought the safety of these procedures into question. However, it is of interest to note that no details regarding the talc preparation were reported and a video-assisted thoracic surgery (VATS) rather than a thoracoscopic procedure was performed with a red-blood-cell (RBC) transfusion rate of 4.5% in the thoracoscopic talc insufflation arm. Therefore, to definitively address the issue of talc safety, a multicenter, open-label, prospective cohort study of 558 patients with malignant pleural effusion undergoing thoracoscopic talc poudrage with 4 g of calibrated large-particle talc was undertaken [4]. The study was designed to address concerns regarding the safety of intrapleural application of talc after rates of acute respiratory distress syndrome (ARDS) of 1–9% were reported in the literature [5]. Indeed, the occurrence of ARDS in some series and its absence in others was independent of the underlying disease, the quantity of talc used or the technique of talc instillation. Several researchers have reported results suggesting that ARDS after talc pleurodesis is mainly related to the particle size of the talc used [6–8], leading to a systemic inflammation [9–11]. In the study carried out by Janssen and colleagues, no patients developed ARDS after thoracoscopic talc insufflation performed by pulmonologists under local (78% of patients) or general (22% of patients) anesthesia using 4 g of calibrated talc in subjects with recurrent malignant pleural effusions [4]. The primary cancer was lung (non-small-cell lung cancer) and breast in 41% and 22% of patients, respectively. Aelony wrote in an accompanying editorial that 'Thoracoscopic talc pleurodesis should be the gold-standard for malignant pleural effusions until controlled observations show a more effective, simpler and equally safe treatment [12].'

In this issue of the European Journal of Cardio-Thoracic Surgery (EJCTS), Mohsen and colleagues report the first prospective comparative study between local iodine pleurodesis (Povidone–Iodine Pleurodesis: PIP) versus thoracoscopic talc insufflation (TTI) in patients with recurrent malignant pleural effusions [13]. Forty-two patients with recurrent malignant pleural effusion, secondary to advanced breast cancer treated by the same chemotherapy protocol and without known allergy to
iodine, underwent after thoracentesis for therapeutic purposes and pleural fluid analysis for biochemical, bacteriological, and cytological evaluation, a VATS procedure under general anesthesia with double lumen intubation. Careful evaluation of the pleural cavity, adhesiolysis if required, and multiple biopsies for histological confirmation were performed before randomization (group A: TTI during VATS followed by tube drainage, group B: single chest tube drainage for lung re-expansion followed by bedside injection of 20 ml of 10% povidone—iodine and 30 ml of normal saline through the tube, which was then clamped for 4 h before re-opening). Patients were followed up every 3 months with clinical assessment for symptom recurrence and chest X-ray. The efficacy of pleurodesis was defined as complete (absence of pleural fluid evaluation), partial (residual pleural fluid or asymptomatic fluid re-accumulation, which did not require thoracentesis), or failure (additional pleural procedures were required). The 30-day evaluation revealed a 9% and 15% failure for TTI and PIP, respectively. Indeed, in a pragmatic and clinical situation, if a patient did not need a repeat ipsilateral pleural intervention following pleurodesis, the outcome should be regarded as successful as this represents the desired outcome from a patient's perspective. The reported success rate at long-term follow-up (4 years) was not significantly different. No statistical difference was found regarding thoracic pain or fever. No cases of respiratory failure after TTI or visual statistical difference was found regarding thoracic pain perspective. The reported success rate at long-term this represents the desired outcome from a patient's perspective. The reported success rate at long-term follow-up (4 years) was not significantly different. No statistical difference was found regarding thoracic pain or fever. No cases of respiratory failure after TTI or visual loss after PIP, as previously described, were reported [14]. The authors concluded that pleural administration of povidone—iodine is efficient for pleurodesis with a good safety profile and that it is a cost-effective alternative sclerosant in countries where talc is not available or contraindicated.

Studies have shown that iodopovidone is effective when administered at the time of thoracoscopy or through a chest tube [15,16]. Experimental studies on animals have demonstrated that intrapleural iodopovidone administration works as an inflammatory agent, which first creates an acute pleural injury followed by inflammation and fibrosis as evidenced by high protein and lactate dehydrogenase (LDH) levels and total white cell count (WCC) [17]. In the article by Olivares-Torres ARDS was reported in 9% of patients after surgical procedures, which included pleural abrasion and PIP administration [15]. In the same publication, the authors also reported severe hypotension and pain due to iodopovidone administration in mesothelioma patients. Visual loss secondary to granular deposition and atrophy occurring in the retinal pigment epithelium has been described after PIP instillation using a high dosage of 10% povidone—iodine [14]. On review of the literature, the complications of PIP appear to be lower when performed without pleural abrasion.

The article by Mohsen and colleagues is another step in finding a safe and efficient alternative to talc for treating patients with recurrent malignant pleural effusions. The major limitation of this interesting clinical study is the small sample size, which does not allow a definitive conclusion to be made regarding the safety and efficacy of PIP compared with talc pleurodesis. As the calculated incidence of ARDS in patients undergoing talc pleurodesis ranges from 0.14% to 0.07%, it would require a study enrolling thousands of patients treated with iodopovidone pleurodesis to demonstrate that it is safer than talc pleurodesis. No conclusion regarding the safety of PIP can be made from a study with 20 patients. The 30-day efficacy between TTI and PIP patients was not statistically significant; however, the trend favored the TTI arm with a 9% failure rate (15% for the PIP arm). The same result was observed during long-term follow-up. The surgical thoracoscopic procedure was used for diagnostic purposes to ensure that both study arms were similar; and the authors concluded that they can safely recommend the bedside procedure based on these results. However, Dresler and colleagues, in their randomized phase III study showed a statistically significant difference in favor of TTI when compared with TS in the subpopulation of malignant effusions secondary to breast cancer (TS: 56 patients – 23%; TTI: 59 patients – 24%) [3]. Therefore, we agree with Mohsen and colleagues that the use of PIP as a potential sclerosing agent should be further assessed in larger studies comparing to other effective sclerosants, especially talc, using the same technical procedure. Even if PIP could be an alternative agent in some countries, talc still remains the ‘gold standard’ for pleurodesis in patients with recurrent malignant pleural effusion due to the short-term and long-term safety, efficacy, and low cost [18]. Plagiarizing a famous advertisement, I would have to say at the present time: ‘Talc for pleurodesis: what else?’

References


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Available online 30 December 2010