Review Article

Pleurodesis: A Review of the Indications, Techniques, and Complications

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Abstract

Pleurodesis is a procedure which obliterates the pleural cavity with the intent of preventing reaccumulation of fluid or air in the pleural cavity. The common indications for performing pleurodesis include malignant pleural effusions and recurrent pneumothorax. Various techniques to perform pleurodesis have been described in the literature. Pleurodesis can be classified as chemical pleurodesis, where in a chemical sclerosant is introduced into the pleural cavity, or mechanical pleurodesis, where in physical abrasion of the pleura is performed during a pleuroscopic intervention. It is important for practicing pulmonary physicians to be abreast with the techniques of performing pleurodesis and its possible complications. The current review article describes the indications of pleurodesis, the technique of performing pleurodesis, possible complications postpleurodesis and their management.

Keywords: *Autologous blood patch pleurodesis, indwelling pleural catheters, iodopovidone, malignant pleural effusions, pleurodesis, recurrent pneumothorax, talc poudrage, talc slurry*

Introduction

Pleurodesis is a procedure that obliterates the pleural space with the aim of preventing recurrent pleural effusion or recurrent pneumothorax. It is performed by inducing inflammation of the pleurae by either instilling a chemical sclerosant or by performing mechanical abrasion. This inflammation leads to fibrosis and symphysis of the parietal and visceral pleurae. All practitioners of pulmonary medicine should be well versed with performing pleurodesis as it is a commonly performed bedside procedure.

Indications

Malignant pleural effusion

This is the most common indication for pleurodesis.[1] Patients diagnosed with malignant pleural effusion (MPE) are candidates for pleurodesis if they satisfy the following criteria:

- The effusion should be symptomatic (producing dyspnea and impairing the quality of life)
- There should be improvement in dyspnea and re-expansion of the lung after removal of the pleural fluid
- The effusion should be rapidly reaccumulating (i.e., requiring therapeutic thoracentesis more than once a month)
- The anticipated survival of the patient should be at least 3 months or above.

When MPE results from a chemosensitive neoplasm (lymphomas, germ cell tumors), pleurodesis is not necessary. Similarly, in patients diagnosed with malignant mesothelioma where radical pleurectomy is being considered, it is advisable not to perform pleurodesis as this will make the surgery technically complicated.

Primary spontaneous pneumothorax

Both chemical and thoracoscopic methods for pleurodesis have been shown to prevent the recurrence in primary spontaneous pneumothorax (PSP). The recurrence rate of pneumothorax after the first episode of PSP is around 30%–50%. Pleurodesis for PSP is indicated in the following circumstances:[2]

- Second episode of PSP (chance of pneumothorax recurrence >60%)
- Persistent air leak following any episode of PSP (lasting >3–5 days)
- Bilateral pneumothorax
- Professions at risk (aircraft personnel, divers).

Whether to perform pleurodesis in the first episode of PSP remains debatable. In a randomized trial on patients requiring

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pigtail catheter drainage for the first episode of PSP, pleurodesis with 300 mg of minocycline has been shown to significantly reduce the recurrence rates when compared to no pleurodesis (29.2% vs. 49.1%).[3] Larger studies are needed to reconfirm this approach.

Secondary spontaneous pneumothorax

Pleurodesis is indicated in all patients with secondary spontaneous pneumothorax (SSP) even in the first episode as there is a high chance of recurrence (>50%) and the recurrence if occurs leads to more physiologic imbalance and can also be life-threatening due to the presence of underlying lung disease.

Nonmalignant refractory effusions

Chemical pleurodesis has also been tried with varying degrees of success (50%–80% success rates) in patients with refractory nonmalignant effusions when the treatment of the underlying disease fails to control the rapid reaccumulation of fluid.[4,5] Some indications include hepatic hydrothorax, uremic effusions, chylothorax, and continuous ambulatory peritoneal dialysis pleural effusions.

Types of Pleurodesis

Pleurodesis can either be-(a) chemical pleurodesis (instillation of a sclerosant into the pleural cavity), or (b) mechanical pleurodesis (abrasion of the pleura or other techniques performed during thoracotomy/video-assisted thoracoscopic surgery [VATS]). The various types of pleurodesis are summarized in Table 1. All the chemical sclerosants act by inducing intense pleural inflammation which in turn leads to the development of adhesions and eventually fibrosis. There is increased local production of cytokines such as interleukin-8, transforming growth factor-beta, and vascular endothelial growth factor.

Table 1: Types of pleurodesis

Chemical pleurodesis
Talc (Talc slurry or Talc poudrage)
Tetracycline derivatives (minocycline, doxycycline)
Silver nitrate
Iodopovidone (betadine)
Anti neoplastic agents (bleomycin, mitoxantrone, nitrogen mustard, cisplatin)
Quinacrine
Immune modulators *(Corynebacterium parvum, Streptococcus pyogenes A3)*
Cytokines (TGF beta)
Mechanical pleurodesis
Mechanical pleural abrasion with dry gauze
Laser abrasion of pleura
Autologous blood patch pleurodesis
Indwelling tunneled pleural catheters (auto-pleurodesis)

TGF: Transforming growth factor

Placement of indwelling tunneled pleural catheters (IPC) is now considered an alternative to chemical pleurodesis in managing MPE.[6] Spontaneous pleurodesis (autopleurodesis) occurs in a subset of people (approximately 50%) with IPCs.[7] The American Thoracic Society and Society of thoracic surgeons recommend either IPCs or chemical pleurodesis as first-line definitive intervention for management of dyspnea in MPE.[8] Compared with chemical pleurodesis, IPC results in shorter hospital length of stay and fewer repeat pleural procedures but carries a higher risk of cellulitis. Careful assessment of individual patient preferences and costs should be considered when choosing between IPC and pleurodesis.[9] A detailed discussion on IPCs is beyond the scope of the current review.

Choice of Sclerosing Agent

An ideal sclerosing agent is one which is easily available and easily administrable, has a high success rate, well tolerated with less adverse reactions and is cost-effective. It should have low regional clearance and a rapid systemic clearance to prevent any systemic adverse effects. Such an agent remains undiscovered and hence, the choice of sclerosing agent depends on local expertise and availability. In India, the three commonly used agents are talc, tetracycline derivatives, and iodopovidone.

Talc pleurodesis

Talc, a trilayered, magnesium sheet silicate is the most effective and most commonly used agent for pleurodesis all over the world. The success rate for talc pleurodesis is around 90%. Various meta-analyses confirmed that talc is superior to other agents for performing pleurodesis.[10,11] Talc used for chemical pleurodesis should be sterile (Steritalc) and graded (<10% of the talc particles should be <10 μ in diameter). There are two methods of talc pleurodesis.

Talc slurry pleurodesis

Talc powder (2–5 g) is dissolved in 80–100 ml of normal saline and is instilled into the pleural space via a chest tube/indwelling pleural catheter. Instillation of 4 g talc slurry via IPC has shown to improve pleurodesis rates as compared to using IPC alone for pleurodesis (43% vs. 23%).[12]

Talc poudrage pleurodesis

Talc powder is sprayed diffusely (as an aerosol) onto the parietal and visceral pleural surfaces under vision using a talc insufflator during a medical thoracoscopy or after a VATS procedure.

Several randomized trials have shown talc slurry and talc poudrage pleurodesis to be equally effective.[13,14] Though some studies have shown talc poudrage to be superior to talc slurry,[10,15] thoracoscopic talc insufflation is more

invasive, has a higher complication rate[14] and may not be feasible in patients with poor performance status. Hence, the choice between these two depends more on the medical circumstance than the difference in efficacy.

Systemic inflammation and acute respiratory distress syndrome (ARDS) (talc induced acute lung injury [TALI]) have been described following talc pleurodesis.[16] These are attributed to the systemic absorption of talc particles through pleural lymphatics. The likelihood of systemic absorption and TALI are more common when the talc particle size is <10 microns and when a high dose is used (>5 g).[17] In our country, steritalc manufactured by Novatech (2, 3, and 4 g) is available which is size calibrated with a median particle diameter of 31.3 μ.

Iodopovidone (betadine) pleurodesis

Iodopovidone is a cost-effective alternative to talc.[18,19] Success rates of >80% were observed in two observational studies.[20,21] In randomized trials, it has been shown to be as effective as talc and superior to bleomycin.[19,22] Pleurodesis is performed by instilling 100 ml of 2% betadine (20 ml of commercially available 10% betadine is diluted with 80 ml of normal saline) into the pleural cavity. Because of the lesser cost and near-universal availability, betadine is commonly used as the agent of choice for pleurodesis in many parts of India.

Tetracycline derivatives

As parenteral tetracycline is no longer available, its derivatives-minocycline and doxycycline are used for pleurodesis. The success rate with these agents is lesser than that seen with talc (60%–70%).[23] The dose of doxycycline for pleurodesis is 500 mg (10 mg/kg body weight) and for minocycline is 300–500 mg. These oral forms must be dissolved in saline and then passed through a 0.2 um sterile and nonpyrogenic polyethersulfone membrane to remove infectious materials and other particulate matter. The main drawback with these agents is the intense pain after the procedure.

Anti-neoplastic agents are less often used for pleurodesis because of their high cost, lesser efficacy as compared to talc, and unfavorable side effect profile. Silver nitrate (20 ml of 0.5% solution) is another cost-effective alternative to talc for pleurodesis.[24,25]

Pleurodesis Procedure

As with any interventional procedure, a written informed consent must be obtained from the patient. The need for the procedure, the steps of the procedure, anticipated complications, and the success/recurrence rates have to be discussed with the patient/family.

Assessing fitness for pleurodesis

Patient should meet the following criteria before pleurodesis is performed.

Draining the pleural space

The pleural effusion or the pneumothorax has to be drained completely by the placement of a chest drain. There is no difference in the outcome of pleurodesis when performed via large-bore drains versus small-bore pigtail catheters.[26,27]

Expansion of the underlying lung

A chest radiograph should be performed before pleurodesis to reconfirm lung expansion. The lung should have expanded and both parietal and visceral pleura should appose each other. Unexpanded lung not only leads to failed pleurodesis but also causes further thickening of the visceral pleura and this will increase the lung entrapment. In the case of loculated MPEs, intrapleural fibrinolysis may be attempted to break the adhesions and drain the pleural space completely before pleurodesis, though the role of these in improving pleurodesis success is debatable.[28-30]

Low chest drain output

Though it is a practice to delay pleurodesis till the daily chest tube drainage decreases to <150 ml per day, recent trials have shown that it is not always necessary.[31] Pleurodesis may be attempted as soon as the lung expands irrespective of the chest drain output. However, in our experience, the chance of successful pleurodesis decreases when the daily chest drain output exceeds 300 ml per day.

Absence of air leak

When performing pleurodesis for patients with pneumothorax, it is preferable to delay the procedure till there is no demonstrable air leak.

Analgesia and sedation

As pleurodesis is a painful procedure it is of utmost importance to ensure patient comfort throughout the procedure. It is preferable to administer parenteral opioid analgesics (fentanyl, pentazocine, tramadol) or anxiolytic/amnestic agents (midazolam) before the initiation of the procedure. Parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) may also be administered for analgesia and have been shown not to decrease the efficacy of pleurodesis.[32]

We also routinely instill intra-pleural lignocaine (20 ml of 1% lignocaine) 15 min before instillation of the sclerosant. British Thoracic Society guidelines recommend instillation of 3 mg/kg lignocaine (maximum dose: 250 mg) before pleurodesis.[33] Patient vital signs need to be monitored before the procedure and for up to 4 h after the pleurodesis.

Administration of the sclerosing agent

Using strict aseptic precautions, the sclerosing agent is reconstituted using normal saline to the desired concentration and volume, and using a 50 ml syringe, instilled into the chest drain. The dose for various commonly pleurodesing agents is given in Table 2. For

Table 2: Dose (s) of commonly available sclerosing agents used for chemical pleurodesis

Sclerosing agent	Dose and dilution
Talc slurry for malignant pleural effusions	4-5 g dissolved in 100 ml normal saline
Talc slurry for pneumothorax	2-3 g dissolved in 100 ml normal saline
Iodopovidone	20 ml of 10% betadine diluted with 80 ml of normal saline (100 ml of 2% solution)
Doxycycline	500 mg (10 mg/kg) diluted in 50-100 ml normal saline
Minocycline	300 mg diluted in 50–100 ml normal saline
Silver nitrate	20 ml of 0.5% silver nitrate solution

patients with a pigtail catheter, it is advisable to attach a three-way adapter which will facilitate easier administration of the agent. Following administration of the agent the tube is clamped for 2–4 h and then unclamped.

Whether to move the patient into different positions after sclerosant instillation to ensure the uniform spread of the sclerosant in the pleural cavity is debatable. Rotation of the patient has not been shown to cause a statistically significant improvement in the pleurodesis success rates.[34]

Removal of the chest drain

The chest tubes are typically left *in situ* till the drain comes to below 150 ml per day. If the output remains high at 48 h, repeat pleurodesis may be attempted. However, evidence suggests that removal of chest drains at 24 h irrespective of the drain output is noninferior to the conventional practice.[35]

Rapid Pleurodesis

One of the major drawbacks of chemical pleurodesis is the need for a prolonged hospital stay (2–5 days). As pleurodesis is a palliative procedure, it is preferable to decrease the hospital stay to as minimum as possible. Two methods of rapid pleurodesis which may be performed as an outpatient procedure have been described.

Technique 1

For free-flowing malignant effusions, a chest drain is placed under image guidance. After complete fluid drainage (reconfirmed by image guidance), talc slurry is instilled within 2 h of drain insertion. After clamping the tube for 30–90 min, the drain is opened for 1–2 h and then removed. The patient is sent back on the same day. This approach has been found to be noninferior to the conventional procedure in two randomized trials.[36,37]

Technique 2

The second technique combines thoracoscopic talc poudrage and the placement of an indwelling tunneled pleural catheter in the same sitting. Patients are sent home on the same day and the catheter is removed once the drain decreases (median duration of catheter– 10 days).[38,39] This approach is more invasive and not cost-effective and hence, may not be feasible in the majority of the centers in the developing world.

Thoracoscopic Poudrage Technique

In patients undergoing medical thoracoscopy, following complete removal of the pleural fluid and removal of any adhesions, talc powder is sprayed uniformly over the pleural surfaces using a dedicated insufflator. All the pleural surfaces are visualized and sequentially sprayed with talc. The appearance of the pleural space as the talc is insufflated is described as the "Sand storm appearance." At the end of the procedure, all the pleural surfaces should have been coated with white talc powder. At the end of the procedure, a chest drain is placed and connected to negative suction (optional). Alternatively, an indwelling tunneled pleural catheter may be placed.

Talc poudrage may also be performed as an add-on procedure following VATS stapling of blebs or wedge resection for management of recurrent pneumothorax. In addition to talc, other agents which have been used for thoracoscopic instillation include betadine solution,[20] bovine dermal collagen powder,[40] and erythromycin powder.[41]

Autologous Blood Patch Pleurodesis

Autologous blood patch pleurodesis (ABPP) is an alternative pleurodesis technique that has been used in patients with persistent air leak with or without complete lung expansion. Studies have shown that ABPP is safe and well tolerated by most patients. A review of 10 retrospective studies reported a success rate of 92%.[42] Randomized trials have shown ABPP to be superior to conservative management (wait and watch) in patients with SSP having persistent air leak who are unwilling for surgery[43] and in patients with persistent air leak following lobectomy.[44]

A sample of the patient's own blood (around 100 mL) aspirated from the cubital vein or the femoral vein is immediately injected into the pleural space via the chest tube followed by 20 mL of saline. The chest tube is not clamped in contrast to the conventional pleurodesis technique. It is left open and hung over an intravenous stand (for 1–2 h) to prevent the development of a tension pneumothorax (because of the presence of underlying air leak). This avoids drainage of blood but allows the air to escape.

The proposed mechanism of action is likely due to direct sealing of the air leak with the clotted blood, as well as the induction of pleural inflammation and eventual pleurodesis. The optimum blood required to achieve successful pleurodesis is unknown and ranges from 50 to

120 ml. Studies have shown that patients who received 100–120 mL of blood achieved closure of air leak faster and more successfully compared to lower blood volumes (50–60 mL).[45,46] Complications occur in <10% of cases and include pleuritis, empyema, and chest tube obstruction. ABPP is the cheapest of all the pleurodesis techniques available.

Assessing Pleurodesis Success

The success of pleurodesis is defined based on the relief of symptoms and preventing recurrence of disease (pleural effusion and pneumothorax). In cases of MPE, the outcome can be classified as:[6]

Complete success

Long-term relief of symptoms related to the effusion, with the absence of fluid reaccumulation on chest radiographs until death.

Partial success

Diminution of dyspnea related to the effusion, with only partial reaccumulation of fluid (<50% of the initial radiographic evidence of fluid) with no further therapeutic thoracenteses required for the remainder of patient's life.

Failed pleurodesis

Lack of success as defined above.

Complications of Pleurodesis

As with any procedure, pleurodesis is not a procedure without complications. Some of the common complications of pleurodesis include:

Pain

Pain is the most common and a near-universal complication of pleurodesis. The intensity of perceived pain varies, depending on the patient's pain perception threshold, the type of sclerosing agent used (higher with tetracycline derivatives), and the underlying disease (higher for pneumothorax as compared to MPE). Systemic and local analgesics can be used to alleviate the pain of pleurodesis.

Use of NSAIDS for analgesia is generally avoided as these are anti-inflammatory and may decrease the efficacy of pleurodesis. However, a recent study demonstrated that the pleurodesis success was not decreased by simultaneous administration of NSAIDs.[32] Similarly, it is prudent to avoid using systemic corticosteroids 24–48 h before the procedure as they are potent anti-inflammatory drugs.

Fever and the systemic inflammatory response

Fever is the second-most common complication and occurs in up to 30% of the patients after pleurodesis. It is a part of the systemic inflammation following the procedure. There may also be a transient leukocytosis. Fever after pleurodesis usually lasts for a couple of days. However, if it persists beyond this period, the possibility of secondary infection needs to be ruled out.

Acute respiratory distress syndrome

This is a potentially life-threatening complication after talc pleurodesis. With the use of sterile size graded talc, the incidence of ARDS has decreased. The chance of ARDS can be minimized if the following precautions are taken: (a) Use of size graded talc with particle size >10 microns, (b) Use no more than 5 g of talc, (c) avoid simultaneous bilateral talc pleurodesis, and (d) avoid talc administration following mechanical pleural abrasion.[47]

Infectious complications

Though uncommon, pleural space infection may occur as a complication when aseptic techniques are not followed. The rate of infections is higher with blood patch pleurodesis as blood serves as a medium for bacterial growth.

Development of loculated effusions (talc loculations)

In some patients, there is the development of loculated pleural collections the following pleurodesis. This is a manifestation of partial pleurodesis with fluid reaccumulation in the nonpleurodesed areas. The loculations gradually disappear with time. Management of such loculated effusions would be symptom-driven.

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Conflicts of interest

There are no conflicts of interest.

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