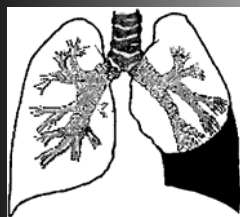


International Pleural Newsletter



A Publication of the International Pleural Network

Volume 3 Issue 1
January 2005

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Pleurodesis for Malignant Pleural Effusions

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Initial reports of pleurodesis to control recurrent pneumothorax or pleural effusions date back to the beginning of the last century. Since then, several agents have been used to produce pleural symphysis. Ideally, the sclerosant should be cost-effective, available worldwide, and easy to manufacture and administer. It should induce minimum morbidity, and be 100% effective. Such an ideal agent does not exist.

Since its description in 1935, talc has been the most widely used agent, with effectiveness >90%. In the initial reports, talc was insufflated by thoracoscopy, and lately delivered in a suspension form ("slurry") via a chest tube. Although intrapleural talc is well tolerated, acute respiratory distress syndrome following talc pleurodesis has been described. Possible explanations for this side effect include absorption and systemic dissemination of contaminants or small-size talc particles, and re-expansion pulmonary edema.

Other substances have been tested as pleurodesing agents. After the production of parenteral tetracycline was suspended, its derivatives, minocycline and doxycycline were widely used. Among the anti-neoplastic agents, bleomycin still stands as the most effective agent (~54% success rate). Nitrogen mustard, cisplatin, cytarabine, doxorubicin, etoposide, 5-fluorouracil, mitoxantrone, and mitomycin-C showed variable results and with significant side effects. *Corynebacterium parvum*, mostly used in Europe, has been abandoned.

OK-432, a cytotoxic agent derived from *S. pyogenes* with antiangiogenic properties, is still used in Asia, with a success rate up to 73%. The antimalarials, particularly quinacrine, is used in Scandinavia with an efficacy comparable with talc.

Silver nitrate (SN), a powerful caustic substance, was the first agent used (in 1901) for pleurodesis. Used in concentrations around 10%, the reported success was >90%.

The *International Pleural Newsletter* is distributed or web-posted by the:

American College of Chest Physicians
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The reason that SN was abandoned is unclear, but probably because of the intense pain it induced. SN meets many of the requirements of an ideal agent: it is inexpensive, available worldwide, and is easily manufactured and instilled. Recent studies have demonstrated the efficacy of 0.5% SN in producing pleurodesis both in experimental and clinical settings. It does not provoke significant pain or mortality and has an effectiveness of ~90%.

In rabbits, silver nitrate produces a sclerosing effect superior to that observed with talc slurry, with more intense fibrin and collagen deposition. A randomized, double-blind study (47 patients with recurrent malignant pleural effusion) using 5g of talc slurry or 20 mL of 0.5% SN showed that talc was effective in 21/24 (87.5%) and SN in 22/23 (95.6%) patients. All patients tolerated the procedure without significant complications.

In recent years, attempts have been made to create pleurodesis with immunologic mediators. Experimental studies have shown that intrapleural injection of transforming growth factor-beta produces a dose-dependant pleurodesis. Other used agents include beta-interferon, interleukin-2 and recombinant tumor necrosis factor, with effectiveness varying from 28 to 87%. However, the application of these agents may be limited by their high cost.

Considering the short life expectancy of patients with malignant pleural effusions, and the urgent need to control their dyspnea, a minimally-invasive bedside procedure is recommended. Ideally, this procedure should be ambulatory, avoiding hospitalization and general anesthesia.

The sclerosing agent can be instilled through a small-bore catheter, avoiding the placement of a chest drain. Commercially available small-bore catheters can easily be introduced into the pleural space. They are well tolerated and can stay in place for weeks allowing periodic draining of the pleural fluid to relieve dyspnea until complete pleurodesis is achieved.

In conclusion, talc, for its efficacy and low cost, should remain a first-line pleurodesis agent. However, more studies are needed to evaluate the safety of talc. If the small size of particles is proven to be responsible for talc-induced ARDS, calibrated and homogeneous talc particles should be used. SN (0.5%) is a promising agent but larger studies are needed to determine its efficacy and side effects. Using small-bore catheters opens a perspective of less invasive procedures. Future studies should focus on cytokines and other inflammatory mediators as novel pleurodesing agents.

References

- Light RW and Lee YCG, eds. Textbook of Pleural Diseases. Arnold, London 2003
- Grodzin CJ and Balk RA. Indwelling small pleural catheter needle thoracentesis in the management of large pleural effusions. Chest 1997; 111:981-88
- Walker-Renard PB, Vaughan LM, Sahn SA. Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994; 120:56-64

- Light RW, Cheng DS, Lee YCG et al. A single intrapleural injection of transforming growth factor-beta 2 produces an excellent pleurodesis in rabbits. Am J Respir Crit Care Med 2000; 162:98-104
- Vargas FS, Teixeira LR, Antonangelo L et al. Experimental pleurodesis in rabbits induced by silver nitrate and talc. 1-year follow-up. Chest 2001; 119:1516-20
- Paschoalini MS, Pereira JR, Abdo EF et al. Silver nitrate versus talc slurry for pleurodesis in patients with malignant pleural effusions. Am J Respir Crit Care Med 1999; 159:A384

Mechanism of Pleurodesis

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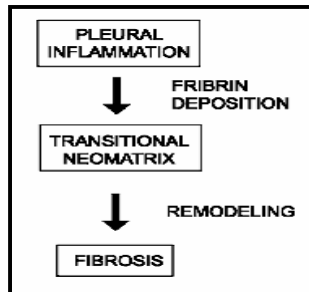
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The mechanism of pleurodesis closely approximates the pathogenesis of wound healing, as previously reviewed¹. In evolving pleurodesis, scar formation with bridging and apposition of the visceral and parietal pleural surfaces evolves through a rapid sequence of inflammation, deposition and remodeling of a transitional neomatrix, and ultimate fibrotic repair. Multiple interactive pathways contribute to the progression of these events and include a wide range of cellular, immunologic and humoral responses.

Derangements of pathways of fibrin turnover play a pivotal role in evolving pleurodesis and other forms of tissue injury (see figure). Increased

microvascular permeability initially occurs as part of the inflammatory response and plasma extravasates into the injured tissues. This process may contribute to formation of exudative effusions. These extravascular fluids are rich in clotting substrates and local



coagulation is initiated by tissue factor that is expressed at the surface of mesothelial cells, fibroblasts and macrophages. Formation of a transitional fibrin neomatrix quickly ensues and fibrinous adhesions that span the visceral and parietal pleural surfaces form loculations that characterize the early stages of evolving pleurodesis².

The transitional matrix undergoes continuous remodeling with invasion by inflammatory cells and fibroblasts. These cells and pleural mesothelial cells elaborate plasminogen activators and matrix metalloproteinases (MMPs) that promote remodeling. Among these effectors, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) can be detected within exudative pleural fluids and contribute to remodeling via proteolysis or cellular signaling. Mesothelial cells may also locally elaborate inhibitors of PAs and the MMPs. With respect to the regulation of fibrin turnover, the balance of PAs and

plasminogen activator inhibitor (PAI) influences local fibrinolytic capacity within the pleural space. The PAs, MMPs and their inhibitors are likewise implicated in the propagation and/or prognosis of various malignancies and their relative expression within the pleural space could theoretically influence tumor burden or risk of recurrent effusion after pleurodesis. These relationships require further investigation.

The expression of uPA, urokinase-type plasminogen activator receptor (uPAR) and PAI-1 by mesothelial and mesothelioma cells has recently been shown to be complex and to involve regulation at the posttranscriptional and transcriptional levels³. Local control of their expression could influence remodeling and fibrotic repair in the pleural space. For example, the efficacy of TGF- β as a pleural sclerosant in preclinical settings may involve further stimulation of PAI-1 as well as collagen production by mesothelial or other resident pleural cell types³⁻⁵. Better understanding of these regulatory pathways may facilitate identification of new strategies that could improve the efficacy of therapeutics to either clear pathophysiologically significant intrapleural loculations or alternatively enhance the efficacy of pleurodesis.

After administration of sclerosing agents, the transitional matrix exhibits deposition of connective tissue as the intrapleural remodeling proceeds during pleurodesis. By 48 hours after intrapleural administration of tetracycline in rabbits, intrapleural fibrinous adhesions begin to exhibit detectable collagen⁶. Over the course of days, the fibrous transformation of the transitional matrix continues with the ultimate formation of mature scar tissue within the intrapleural compartment, leading to clinically effective pleurodesis.

References

1. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *New Engl J Med* 1986; 315:1650-9.
2. Idell S, Mazar A, Cines D, et al. Single-chain urokinase alone or complexed to its receptor in tetracycline-induced pleuritis in rabbits. *Am J Respir Crit Care Med* 2002;166:920-6.
3. Idell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. *Crit Care Med* 2003; 31:S213-S220.
4. Lee YCG, Lane KB, Zoia O, et al. Transforming growth factor-beta induces collagen synthesis without inducing IL-8 production in mesothelial cells. *Eur Respir J* 2003; 22:197-202.
5. Marchi E, Teixeira LR, Vargas FS. Management of malignancy-associated pleural effusion: current and future treatment strategies. *Am J Respir Med* 2003; 2:261-73.
6. Miller EJ, Kajikawa O, Pueblitz S, et al. Chemokine involvement in tetracycline-induced pleuritis. *Eur Respir J* 1999; 14:1387-93.

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Indwelling Catheter for Malignant Effusions

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Symptomatic malignant pleural effusions are most commonly managed by chemical pleurodesis. The primary disadvantage of chemical pleurodesis is that it requires hospitalization for approximately five days.

An alternative to chemical pleurodesis is insertion of an indwelling catheter. The catheter that is most commonly used (Pleurx catheter) is a 15.5Fr silicone rubber catheter that can be inserted on an outpatient basis^{1,2} by pulmonologists, surgeons, or interventional radiologists. The catheter is tunneled and has a valve on the distal end that prevents fluid or air from passing in either direction through the catheter unless the catheter is accessed with the matched drainage line. Pleural fluid is drained at 24 to 48 hour intervals by inserting the access tip of the drainage line into the valve of the catheter and then draining the fluid via an external tube into vacuum bottles³.

In the original multicenter study, comparing the indwelling catheter with chemical pleurodesis with doxycycline 500mg, 144 patients with malignant pleural effusion were randomized to receive one of the two treatments³. The degree of symptomatic improvement was similar in both groups as was the life expectancy³. However, the median one day hospitalization time for the group with the indwelling catheter was significantly less than that of 6.5 days in the doxycycline group³. At the present time the catheter is frequently inserted in an outpatient setting.

Interestingly, the presence of the indwelling catheter will lead to a spontaneous pleurodesis in proximately 20 - 50% of patients^{2,4}. The pleurodesis occurs at a median of 25 days after the catheter is inserted and is more likely to occur if the amount of pleural fluid drainage is decreasing. The mechanism for this spontaneous pleurodesis is not known.

The morbidity from the indwelling catheter is relatively low. In the initial study³, in-hospital morbidity occurred in 10 of 96 patients and included fever (n=3), pneumothorax (3), misplacement of the catheter (2), re-expansion pulmonary edema (1), and hypercapnic respiratory failure due to over sedation (1). In the 90-day follow-up period, three patients developed tumor seeding of the catheter tract that did not require therapy, six patients developed cellulitis around the catheter tract that responded to oral antibiotics, and seven patients reported pain during fluid drainage. In some patients the pleural fluid became loculated with time decreasing the effectiveness of the indwelling catheter. In another study of 100 patients receiving the pleural catheter, pleural infection developed in five patients¹.

In conclusion, an indwelling pleural catheter is a viable alternative for the management of patients with symptomatic malignant pleural effusion. Its primary advantage compared

to chemical pleurodesis is that the procedure can be performed on an outpatient basis. The recently published British Thoracic Society guidelines for the management of malignant pleural effusions concluded that “an indwelling pleural catheter is an effective option for controlling recurrent malignant effusions when length of hospitalization is to be kept to a minimum and expertise and facilities exist for outpatient management of these catheters”⁴.

References

1. Putnam JB Jr, Walsh GL, Swisher SG, et al. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. *Ann Thorac Surg* 2000;69:369-75.
2. Pollak JS, Burdge CM, Rosenblatt M, et al. Treatment of malignant pleural effusions with tunneled long-term drainage catheters. *J Vasc Interv Radiol* 2001;12:201-8.
3. Putnam JB, Light RW, Rodriguez MR, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. *Cancer* 1999;86:1992-1999.
4. Antunes G, Neville E, Duffy J, et al. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; 58 Suppl 2:II29-II38.

Trapped Lungs

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Definition and Mechanism: A pleural effusion is said to be due to a trapped lung when the effusion is persistent with no apparent cause other than mechanical restriction of the visceral pleura preventing lung expansion¹. Patients with malignant pleural effusions occasionally have a trapped lung². With trapped lung there is no alternate explanation other than mechanical restriction of lung expansion for the persistence of pleural effusion. Trapped lung can result from fibrinous or granulomatous pleuritis^{3,4}.

Pathophysiology: The responsible process must have caused pleural inflammation that persisted long enough for the mature fibrous membrane to develop over the visceral pleura. This membrane does not allow the lung to expand to the chest wall. A negative pressure is created between the chest wall and the non-expanding lung, and fluid migrates into the pleural space due to the negative pressure^{4,5}.

Etiology: Trapped lung can be observed under the setting of a malignant or a non malignant disease.⁵ The initial event producing the pleural inflammation is usually a pleural infection or a hemothorax, but can be a spontaneous pneumothorax, thoracic operations (particularly CABG surgery), uremia, collagen vascular disease, histoplasmosis or tuberculous pleurisy⁴. The frequency of trapped lung with malignant pleural effusion appears to be greatest with underlying mesothelioma or primary lung cancer².

Presentation: Trapped lung usually presents as an asymptomatic, chronic, unilateral pleural effusion. Occasionally, patients present with dyspnea, restrictive dysfunction on pulmonary function testing, and no other apparent cause of their dyspnea⁴. The pathognomonic radiographic sign is the pneumothorax *ex vacuo*, after evacuation of the effusion in association with thickened visceral pleura³ (see figure).

Chest radiograph of a patient with a trapped lung. The lung failed to re-expand despite the insertion of a chest tube.



Diagnosis: The diagnosis of pleural effusion due to trapped lung should be suspected in any patient with a stable chronic pleural effusion, particularly if there is a history of pneumonia, pneumothorax, thoracic surgery, or hemothorax⁴. If the lung does not expand after drainage of an effusion with low LDH and protein levels, a visceral pleural membrane is present, and endobronchial disease and severe parenchymal disease are absent, a presumptive diagnosis of trapped lung can be established.

A trapped lung can be suggested by any of the following criteria in the absence of endobronchial obstruction: 1) failure of the lung to expand completely after most of the fluid has been removed by therapeutic thoracentesis, as demonstrated by chest radiograph; 2) an initial pleural fluid pressure of <-5cmH₂O; 3) a decrease in pleural fluid pressure to <-20mmHg after one liter of fluid is removed; or 4) a pleural space elastance >19cmH₂O when removing 500mL of fluid⁴. If the fluid is an exudate, active pleural disease is usually present. However, trapped lung can only be diagnosed with certainty after successful decortication⁵.

Management: The development of trapped lung can be prevented with appropriate management of the pleural space during the acute inflammatory phase of most contributing conditions. Trapped lung in the asymptomatic patient does not require therapy. There is no role for serial thoracentesis, since the pleural effusion recurs rapidly after each thoracentesis. Decortication should be considered if the patient remains dyspneic after all other causes of dyspnea have been excluded or successfully treated.

References

1. Doelken P, Sahn SA. Diagnosis and management of trapped lung. *PCCU*, Vol 16: lesson 21.
2. Light RW. Diagnosis and management of trapped lung. *UpToDate* 2004, Feb27.
3. Plataki M, Bouros D. Iatrogenic and Rare Pleural Effusions. In: Bouros D, ed. *Pleural Disease*. Markel Dekker, New York 2004, 186; 897- 913.
4. Sahn SA. Malignant Pleural Effusions. In: Bouros D, ed. *Pleural Disease*. Markel Dekker, New York 2004, 186; 411-38.
5. Light RW. *Pleural Diseases*, 4th ed. Lippincott, Williams, and Wilkins, Baltimore, 2001.