

Adjunct strategies to enhance the efficacy of indwelling pleural catheters

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Abstract Malignant pleural effusion remains a distressing and unfortunately common occurrence. Pleural palliation should be focused on relieving dyspnea with as few procedures as possible. The introduction of the indwelling tunneled pleural catheter has been shown to fulfill these goals; however, it is not without limitations. The ability to potentially combine the results of a long-term pleurodesis procedure without the need for a prolonged hospitalization remains an attractive option. While no large-scale trials have been completed nor is there widespread acceptance, the introduction of “rapid” or “accelerated” pleurodesis procedures, often using tunneled indwelling pleural catheters, have the potential to significantly change the current paradigm of malignant pleural effusion management. This article reviews the current data available for “rapid” and “accelerated” pleurodesis protocols and their outcomes.

Keywords Malignant pleural effusion · Pleurodesis · Rapid pleurodesis · Accelerodesis · Aggressive pleural drainage · Indwelling tunneled pleural catheter

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Introduction

Malignant pleural effusion (MPE) affects more than 150,000 patients each year within the USA [1] with lung and breast carcinomas being the most common cancers complicated by MPE [2, 3]. The development of MPE can frequently lead to debilitating dyspnea, which may significantly impact upon a patients’ functional status and quality of life [1, 2, 4, 5].

Current options for MPE management are targeted toward palliation as the development of a MPE usually represents incurable, metastatic disease. The more commonly utilized available therapeutic options include the following:

- Pharmacologic agents to palliate the sensation of dyspnea (i.e., oxygen and morphine)
- Repeated pleural drainage via thoracentesis
- Tube thoracostomy drainage with instillation of a sclerosant to induce pleurodesis
- Indwelling tunneled pleural catheter (IPC) placement
- Thoracoscopy with sclerosant instillation to induce pleurodesis

Pleural palliation should be offered to all patients presenting with MPE who demonstrate symptomatic relief after pleural drainage. Current British Thoracic Society and American College of Chest Physicians guidelines promote definitive procedures to achieve this goal, namely a pleurodesis procedure or placement of an IPC due to the known high rate of recurrence in MPE with simple thoracentesis [2, 5]. Previous guidelines have often recommended sclerosant-induced pleurodesis as the procedure of choice for MPE management [1, 4], but data continue to accrue regarding the benefits of IPCs [6, 7], and newer guidelines have recognized the importance and benefits of IPC placement [2, 5]. In patients with trapped lung physiology, the placement of IPC remains the treatment of choice [2, 5].

Current use of pleurodesis and IPC

While treatment options exist for MPE management, each clearly has its advantages and disadvantages that must be considered. The placement of an IPC commits patients to the long-term management of an indwelling catheter and potential complications such as infection [6, 8, 9, 10], catheter blockage [6, 10], and metastatic disease at the catheter site [11]. Although many of these complications are not life-threatening and may not require hospitalization, they often represent a need for repeated healthcare interactions with associated cost escalation, potentially undermining the purpose of an ambulatory drainage system. While pleurodesis procedures (either via poudrage or slurry) may represent a definitive procedure, they are unfortunately not always successful or free from complications. A significant disadvantage to pleurodesis remains the requirement for hospitalization, operating room costs (if performed in association with thoracoscopy), as well as a 3–14 % risk of respiratory complications when using non-graded talc [12, 13]. In patients with a median survival of 3–6 months, the need for a week of hospitalization may represent almost 10 % of their remaining lifetime. This potential impact may again defeat a major goal of pleural palliation.

As a result of these issues, research into improving current MPE management persists. The ideal pleural palliative procedure would possess the following qualities:

- Effective relief of dyspnea
- Outpatient performance (or potentially very limited hospital stay (<24 h))
- Minimal need for re-intervention/limitation of contact with the healthcare system
- Minimal adverse effects
- Cost-effective

Current research and potential advances in MPE management appear to involve attempts at hastening the pleurodesis process, allowing it to occur as an outpatient, or with minimal hospitalization times. The three most promising theories involve the use of more aggressive ambulatory pleural drainage, performance of “rapid pleurodesis” procedures, and the use of sclerosant-coated IPC’s to promote pleurodesis.

Aggressive pleural drainage

One of the disadvantages of IPCs for MPE management remains the requirement for ongoing care of an indwelling catheter as well as the costs associated with prolonged drainage. Promoting early spontaneous pleurodesis and therefore early removal of the IPC address both of these concerns.

Spontaneous pleurodesis is often identified by the presence of decreased IPC fluid output (<50–100 mL) on three

consecutive drainages without radiographic or symptomatic recurrence of pleural effusion [14, 15]. The occurrence of spontaneous pleurodesis has been reported in multiple studies after IPC placement, and rates of spontaneous pleurodesis appear to vary between studies. The largest systematic review to date examined 943 patients undergoing IPC placement with 45.6 % achieving spontaneous pleurodesis, on average, 52 days post insertion [10].

While the mechanism of spontaneous pleurodesis during IPC placement remains unclear, some believe that the presence of foreign material may promote inflammation and a subsequent pleural reaction when the pleural space is emptied on a frequent basis [2]. Others have theorized that the continued and aggressive drainage of the pleural space may lead to sustained inflammation during pleura-pleura apposition and increased spontaneous pleurodesis rates [16].

Current recommendations for pleural drainage after IPC placement are lacking, as evident by the reported drainage schedules in the literature. Drainage schedules may range from daily to only with the development of symptoms [14, 15–18]. No drainage schedule patterns have been directly compared. Examples of initial drainage patterns include, “... three times weekly at home, allowing flexibility in the frequency and volume drained according to symptoms...” [14].

Questions regarding particular drainage schedules and subsequent outcomes remain, which have promoted further research. Two current studies are registered on the ClinicalTrials.gov website [19, 20] that examine the role of different drainage schedules and the subsequent rates of pleurodesis. The first study [19] is a multicenter, randomized trial comparing the impact of aggressive (daily) versus standard (every other day) IPC drainage. The primary endpoint chosen was the rate of spontaneous pleurodesis at 2, 6, and 12 weeks, and approximately 150 patients were enrolled. At the time of writing, this trial has completed accrual and awaiting results of publication. The second study [20] is also a randomized, open-label trial comparing daily to thrice weekly IPC drainage. The primary endpoint chosen was the time to spontaneous pleurodesis with an estimated enrollment of 250 patients. Both studies have interestingly defined the use of once daily drainage as aggressive with slightly differently defined standard therapies and primary endpoints.

It remains unknown if more aggressive drainage will induce early spontaneous pleurodesis and retard pleural fluid reaccumulation; hopefully, these two trials will provide an answer. As the final data is not available, we must remain mindful of the economic impact that daily drainage may incur. As the use of drainage bottles appears to represent the larger, long-term drainage cost associated with IPC use [21–23], conversion to a daily drainage protocol may significantly increase the cost burden, depending on the total number of bottles used

Table 1 Review of the current literature of self-proclaimed “Rapid Pleurodesis” protocols

Author	Year	Title	Intervention	Patients	Primary outcome	Tube removal	Hospital days	Pleurodesis success rate	Complications	Comments
Reddy	2011	Rapid Pleurodesis for Malignant Pleural Effusions: A Pilot Study	Medical thoracoscopy, IPC placement, 5 g talc poudrage, tube thoracoscopy drainage	30 patients	Observational study—reduce hospital stay, reduce IPC days, and improve quality of life	Tube thoracoscopy—1 day, IPC—7.54 days	1.79 days	24/26 (92 %) at 6 months	Fever (2), empyema (1), repeat pleural intervention (1)	Aggressive IPC drainage (POD#1—T1D, POD#2 and 3—B1D, POD#4 and beyond—qDay)
Folch	2011	Rapid Pleurodesis: An Outpatient Alternative	Medical Thoracoscopy, IPC placement, 4–6 g talc poudrage	8 patients	Retrospective study comparing outcomes to Reddy et al. study	IPC—16 days	1 day	n/a	0	
Porcel	2006	Rapid pleurodesis with doxycycline through a small-bore catheter for the treatment of metastatic malignant effusions	12 French tube thoracoscopy, 500 mg doxycycline	34 patients, 2 patients underwent bilateral placement for total of 36	Observational study—reduce tube thoracoscopy days, pleurodesis rates	24 h—25/36, 48 h—34/36	n/a	25/31 (81 %) in those surviving more than 30 days	Pain (13), fever (3), pneumothorax (2)	
Yildirim	2005	Rapid pleurodesis in symptomatic malignant pleural effusion	12 French tube thoracoscopy, 35 mg/kg oxytetracycline, randomized to receive one-time dose of oxytetracycline versus fractionated oxytetracycline dose delivered every 6 h	27 patients, 12 in standard group, 15 in fractionated group	Randomized trial to reduce hospital stay, also collected pleurodesis data at 6 months	Standard group—7 days, fractionated group—1.9 days	Standard group—8.3 days, fractionated group—2.3 days	At 6 months—one failure in each group	n/a	
Spiegler	2003	Rapid Pleurodesis for Malignant Pleural Effusions	14 French tube thoracoscopy, sclerosing agent delivered (talc or bleomycin)	29 chest tube insertions	Prospective case series identifying pleurodesis failure at 4 weeks	All tubes clamped for 90 min after sclerosing agent delivered, drained for 2 h then removed	n/a	Complete response—14/29, partial response—9/29	Pain (3), fever (2), pneumothorax (1)	
Sartori	2004	Sonographically Guided Small-Bore Chest Tubes and Sonographic Monitoring for Rapid Sclerotherapy of Recurrent Malignant Pleural Effusions	9 French tube thoracoscopy, bleomycin 0.75 mg/kg, repeat injection given if persistent fluid output after 12 h	50 patients	Pleurodesis rate	Procedure and tube removal completed within 24 h—29 patients; within 48 h—21 patients	n/a	42/50 (84 %) with complete or partial response at 30 days	Fever (24), vomiting (6), chest pain (8)	In those with loculated fluid, additional thoracentesis procedures were performed followed by local bleomycin delivery
Hsu	1998	Ultrasound-guided Small-bore Elecath Tube Insertion for the Rapid Sclerotherapy of Malignant Pleural Effusion	12 French tube thoracoscopy, 60 IU bleomycin	20 patients, with 2 patients undergoing bilateral procedures for a total of 22	Pleurodesis rate at 30 days	Median time to removal—2 days	n/a	17/22 (77 %) with complete or partial response at 30 days	Fever (17), vomiting (3), hiccups (1)	After placement of tube, 6 patients were excluded from procedure due to lack of lung re-expansion

(i.e., more bottles over a shorter duration vs. fewer bottles over a longer duration).

Rapid pleurodesis

The true definition of “Rapid Pleurodesis” is not readily apparent within the literature; however, it appears to define a pleurodesis procedure that is not associated with the traditional 5–7 days of tube thoracostomy drainage and hospital stay. In some articles, it appears related to the in situ dwell time of the pleural drainage catheter [24–27], whereas in others, it appears related to the duration of tube thoracostomy drainage with inpatient hospitalization [28–30]. No large randomized trials have been performed utilizing a rapid pleurodesis protocol, nor is the literature specific about a particular protocol of rapid pleurodesis. Table 1 offers a review of the current literature of self-proclaimed “Rapid Pleurodesis” protocols.

As mentioned previously, the long-standing problem with pleurodesis remains the requirement for inpatient management of tube thoracostomy drainage. Subjecting end-stage cancer patients to hospital admission and all its subsequent complications remains undesirable. Attempts to reconcile this problem have been addressed in a number of ways.

Initial studies of rapid pleurodesis describe the use of small-bore catheters for pleural drainage, followed by early tube removal, usually within the first 24–48 h and frequently without regard for the current pleural fluid output. Very little data are available regarding the impact these procedures have on hospitalization; however, one would assume that patients admitted with dyspnea related to MPE, the early evacuation of effusion and sclerotherapy may permit for faster discharge than the traditional 5- to 7-day protocols. Pleurodesis success rates within these cohorts seem reasonable, with successful pleurodesis rates reported in the 80 % range or better in each study [24–27, 29].

Two more recent studies use a different description of rapid pleurodesis (Fig. 1, Video 1). They describe the use of medical thoracoscopy with IPC placement followed by talc poudrage [28, 30]. Both series recorded overall tube drainage (often only the IPC drainage on an ambulatory basis) and total

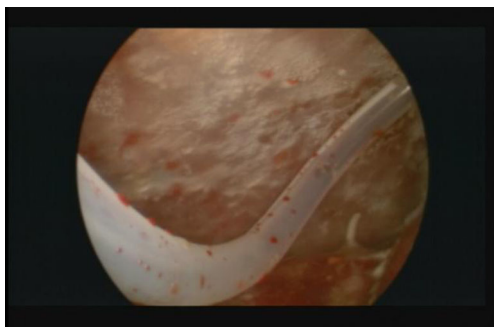


Fig. 1 A recent studies use a different description of rapid pleurodesis

hospital days. The median hospital stay ranged from 1 to 1.8 days with IPC removal occurring at 7.5–16 days. This significant reduction in hospital days required for pleurodesis as well as the duration with IPC in situ before onset of pleurodesis can potentially offer benefits in healthcare costs and quality of life.

These time and cost benefits remain theoretical at this point. No large prospective trials have been performed utilizing this approach; however, one is currently recruiting. Clinical trial NCT00758316 is attempting to randomize patients to talc poudrage versus talc poudrage and IPC placement, assessing pleurodesis rates, hospitalization times, complication rates, and quality of life scores [31].

Accelerodesis

The notion of “accelerodesis” has not been well accepted into the current management options for MPE, as evident by its lack of prominence within review articles on the subject. However, the hastening of pleurodesis during IPC usage appears to show promise. The term “accelerodesis” is currently under patent protection by Carefusion, Inc. [32]; therefore, its design and current iterations are somewhat limited.

The available data on “accelerodesis” are limited to animal models. Two animal studies by Trembley et al. have demonstrated the successful delivery of a low-dose sclerosant (silver nitrate) over a prolonged time course achieving subsequent pleurodesis [33, 34]. The initial study utilized a rabbit model during which silver nitrate was delivered over a 1, 5, and 14 day schedule in order to help determine the feasibility and effectiveness for intrapleural administration. A low dose of 0.05 % silver nitrate was able to achieve an effective pleurodesis score when examined histologically at autopsy [33]. A follow-up study by the same group utilized a rabbit and lamb model to help determine the effectiveness of a chitosan-silver nitrate-hyaluronic acid hydrogel-coated pleural catheter. In both animal types, the silver nitrate-coated catheters were placed for a total of 14 days and subsequently removed. Both studies demonstrated successful pleurodesis results from visual inspection and histologically. This low-dose, prolonged delivery system may help obviate the need for a large single-dose delivery of drug and the resultant associated adverse events.

Marchi et al. first identified that low-dose sequential dosing of sclerosants such as silver nitrate and talc caused effective pleurodesis; however, his initial outcomes were related to markers of systemic inflammation [35, 36]. Trembley et al. identified that the use of silver nitrate could be delivered over 1, 5, or 14 days and still achieve effective pleurodesis, despite the use of an overall lower daily dosage [33]. The use of low-dose silver nitrate appears to result in a lower systemic response (white count elevation, neutrophils, vascular

endothelial growth factor levels, etc.) compared to higher doses [35, 36], potentially allowing for a safer pleurodesis procedure. Trembley et al. have gone on to demonstrate the successful use of a silver nitrate-coated IPC within rabbit and sheep models. They concluded that the use of a coated IPC to promote “accelerodesis” may retain the advantages of IPC placement (minimally invasive, outpatient) while increasing earlier and successful pleurodesis rates [34].

As noted above, the concept of accelerodesis has only been tested in animals, and no human studies are currently available. A study involving the use of an IPC coated with silver nitrate (a known effective sclerosant agent) is currently in the early planning stages [personal communication]. While silver nitrate is being tested, the use of any sclerosant agent (talc, bleomycin, silver nitrate, etc.) could potentially be placed on the IPC and subsequently within the pleural space to help promote spontaneous pleurodesis.

Conclusion

The debate between IPC use and pleurodesis remains a common one, and rightfully so as both procedures have their own limitations. Current research attempting to combine the benefits of both procedures is exciting. The creation of a procedure that can improve outcomes by decreasing hospital stay, reducing costs, and increasing spontaneous pleurodesis rates is an active field of MPE research. The authors remain excited about the renewed research interest in MPE management and the future impact we may be able to offer for this oftentimes debilitating disease.

Compliance with ethics guidelines

Conflict of interest Dr. Christopher Gilbert has no conflict of interest to disclose.

Dr. David Feller-Kopman reports personal fees from CareFusion, during the conduct of the study.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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