ORIGINAL ARTICLE

Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions

The ASAP Trial

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Abstract

Rationale: Patients with malignant pleural effusions have significant dyspnea and shortened life expectancy. Indwelling pleural catheters allow patients to drain pleural fluid at home and can lead to autopleurodesis. The optimal drainage frequency to achieve autopleurodesis and freedom from catheter has not been determined.

Objectives: To determine whether an aggressive daily drainage strategy is superior to the current standard every other day drainage of pleural fluid in achieving autopleurodesis.

Methods: Patients were randomized to either an aggressive drainage (daily drainage; n = 73) or standard drainage (every other day drainage; n = 76) of pleural fluid via a tunneled pleural catheter.

Measurements and Main Results: The primary outcome was the incidence of autopleurodesis following the placement of the indwelling pleural catheters. The rate of autopleurodesis, defined as complete or partial response based on symptomatic and radiographic changes, was greater in the aggressive drainage arm than the standard drainage arm (47% vs. 24%, respectively; $P = 0.003$). Median time to autopleurodesis was shorter in the aggressive arm (54 d; 95% confidence interval, 34–83) as compared with the standard arm (90 d; 95% confidence interval, 70 to nonestimable). Rate of adverse events, quality of life, and patient satisfaction were not significantly different between the two arms.

Conclusions: Among patients with malignant pleural effusion, daily drainage of pleural fluid via an indwelling pleural catheter led to a higher rate of autopleurodesis and faster time to liberty from catheter.

Clinical trial registered with www.clinicaltrials.gov (NCT 00978939).

Keywords: malignant pleural effusions; indwelling pleural catheter; pleurodesis

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At a Glance Commentary

Scientific Knowledge on the Subject: Patients with malignant pleural effusions have significant dyspnea and shortened life expectancy. Indwelling pleural catheters allow patients to drain pleural fluid at home and can lead to autopleurodesis. The optimal drainage frequency to achieve autopleurodesis is not known.

What This Study Adds to the Field: Daily drainage of pleural fluid via an indwelling pleural catheter in patients with malignant pleural effusions, as compared with every other day drainage, led to more rapid and frequent autopleurodesis.

Malignant pleural effusions cause significant morbidity in patients with advanced lung cancer, primary pleural tumors, or metastatic extrathoracic malignancies. Patients are often symptomatic with shortness of breath, cough, or chest pain and have a short life expectancy with a median survival of 3 to 12 months based on the type of the cancer (1). Current management options are centered on symptomatic improvement and include repeated thoracentesis, chemical pleurodesis via tube thoracostomy or thoracoscopy, indwelling pleural catheter (IPC), and, rarely, surgical decortication (2).

The IPC was introduced in the late 1990s as a less invasive and effective alternative to chemical pleurodesis (3). It involves placement of a silicone catheter with its distal part residing in the pleural space, middle part tunneled under the skin and soft tissue, and proximal part laying outside the body and accessible for drainage. The proximal hub of the catheter has a self-sealing valve access that can be connected to disposable vacuum bottles allowing intermittent drainage of pleural fluid on an outpatient basis.

Data gradually emerged showing the IPC to be a viable outpatient management option for patients suffering from malignant pleural effusions with high success in relief of dyspnea and low complications rate (4–11). Randomized controlled studies, comparing IPC with chemical pleurodesis using talc or doxycycline via tube thoracostomy, found them equally effective in relieving dyspnea with the added advantage of outpatient placement and management (3, 12, 13). Autopleurodesis, defined as spontaneous cessation of pleural drainage without instillation of a chemical agent in the pleural space and relief of dyspnea, was achieved in 46–51% of patients with IPC (3, 12).

Although the use of IPC rapidly expanded in the last decade (14), questions remain about optimal frequency of drainage and its impact on achievement of autopleurodesis; adverse events (AEs), such as infection; and patient tolerability of frequent outpatient-based drainage. The primary objective of this trial was to compare an aggressive daily drainage strategy with the current standard every other day drainage of pleural fluid in achieving autopleurodesis, with secondary objectives of time to autopleurodesis (TTAP), quality of life, satisfaction of patients and caregivers, and AE rate.

Methods

Study Design

We performed a randomized, single-blinded, phase IV, multicenter clinical trial at 12 centers in the United States from 2009 to 2013 (the ASAP [Impact of Aggressive versus Standard Drainage Regimen Using a Long-Term Indwelling Pleural Catheter] trial). The sponsor was Duke University, which received an unrestricted grant from CareFusion, Inc. The trial was designed by investigators at Duke University, National Jewish Health, Vanderbilt University, and Washington University in St Louis. Participating institutions included Duke University, Lahey Hospital and Medical Center, Beth Israel Deaconess Medical Center in Boston, Johns Hopkins University, National Jewish Health, University of Utah, Emory University, Virginia Commonwealth University, Anne Arundel Medical Center, Saint Elizabeth Medical Center in Boston, Yale University, and Mayo Clinic.

The study management, monitoring, data maintenance, and statistical analysis were conducted at Duke University. The authors vouch for the accuracy and completeness of the data and analyses. The study was conducted in accordance with the trial protocol and was approved by the institutional review board in all participating centers before recruitment began.

Patients

Eligibility criteria required that patients be 18 years or older with a diagnosis of a recurrent pleural effusion in the setting of known malignancy with either a confirmed malignant involvement of the pleural space by fluid cytology or pleural biopsy or a recurrent pleural effusion with no other identifiable cause after a thorough work-up. Patients had to be symptomatic from the pleural effusion (shortness of breath, cough, or chest pain), demonstrate symptomatic improvement after therapeutic thoracentesis, and have recurrent symptoms with recurrence of the pleural effusion following the therapeutic thoracentesis.

Exclusion criteria included projected life expectancy less than 30 days as predicted by Karnofsky Performance Status (KPS) score less than 30, radiographic evidence of trapped lung (persistent lung collapse with failure of the lung to reexpand on chest radiograph [CXR] following drainage of a pleural effusion), loculated pleural effusion, previous surgery or attempted pleurodesis on the affected side, presence of chylothorax or pleural infection, inability to adequately perform pleural drainage at home, uncorrectable bleeding disorder, skin infection at the site of intended catheter insertion, and pregnancy.

Randomization and Blinding

A randomized block design within strata defined by treatment center was used to randomize patients with equal allocation to study arms. Patients at each center were randomized by calling the study coordinator at the coordinating center (Duke University).

The treating physician, patient, and study coordinator were not blinded to the treatment allocation. Interpretation of chest radiographs and management decisions were performed independently by the treating physician. Additional review of CXR studies, obtained at any point in the study, was performed by an independent blinded pulmonologist. This reviewer scored all CXRs on anonymized CDs without knowledge of patient's identity, date and time of the examination, drainage history, or treatment arm. The radiographs were scored on a scale of 0–5 as follows: 0 = no effusion, 1 = blunting of the costophrenic angles, 2 = blunting up to 25% of the hemithorax, 3 = effusion size 26–50% of the hemithorax, 4 = effusion size 51–75% of

the hemithorax, and 5 = effusion size 76–100% of the hemithorax. The score of the radiograph was a component in the ultimate classification of the primary outcome as complete, partial, or failed autopleurodesis.

Study Procedures

Drainage of pleural fluid was performed at home by a visiting nurse or a family member (after attending an education session at the time of placement and given written instruction) using vacuum bottles that can be attached to the catheter via a drainage line (PleurX catheters; CareFusion, Inc., San Diego, CA). Patients randomized to the standard drainage arm were instructed to drain a maximum of 1 L of pleural fluid via the supplied vacuum bottles every other day. Patients in the aggressive arm were instructed to drain a maximum of 1 L of pleural fluid via the supplied vacuum bottles on a daily basis. In either group, drainage was stopped if cessation of pleural fluid flow occurred or patient developed persistent cough, shortness of breath, chest tightness, or chest pain.

Outcomes

Primary End Point

The primary end point was the incidence of autopleurodesis following the placement of an IPC. Autopleurodesis was reached with either complete response (CR) or partial response (PR).

Possible outcomes by end of study period, at 12 weeks after insertion, included CR, PR, lack of response, or death. Patients who could not meet the 12-week end time point because of patient factors or catheter/disease factors necessitating catheter removal were marked as "unable to complete study" and their data were included in the analysis up to the point where they left the study.

CR was defined as a decline in the quantity of pleural fluid to less than or equal to 50 ml on three consecutive attempted drainages, radiographic scores of 0–1, and lack of symptoms (shortness of breath, cough, or chest pain). PR was defined the same except for a radiographic score of 2–5. Lack of response was defined as failure to achieve autopleurodesis by 12 weeks with the patient continuing to drain fluid via the catheter.

IPCs can become clogged with clots or fibrin and cease to function as a drainage conduit. To differentiate catheter dysfunction from autopleurodesis, patients with drainage

Table 1. Baseline Patient Characteristics

Variable	Study Arm	
	Aggressive (*n* = 73)	Standard (*n* = 76)
Sex, n (%)		
Female	42 (58)	52 (68)
Male	31 (42)	24 (32)
Race, n (%)		
White	57 (78)	60 (79)
Black	13 (18)	13 (17)
Other	3 (4)	2 (2)
Comorbidities, n (%)		
Anemia	8 (11)	11 (14)
Asthma	4 (5)	2 (3)
Cerebrovascular accident	2 (3)	0 (0)
Chronic kidney disease	0 (0)	6 (8)
Chronic obstructive pulmonary disease	5 (7)	7 (9)
Coagulopathy	0 (0)	1 (1)
Congestive heart failure	2 (3)	4 (5)
Coronary artery disease	6 (8)	7 (9)
Diabetes	15 (21)	16 (21)
Deep venous thrombosis/pulmonary embolism	9 (12)	4 (5)
Hyperlipidemia	18 (25)	18 (24)
Hypertension	24 (33)	40 (53)
Hyperthyroidism	2 (3)	1 (1)
Hypothyroidism	8 (11)	12 (16)
Idiopathic pulmonary fibrosis	2 (3)	0 (0)
Nephritic syndrome	0 (0)	1 (1)
Peptic ulcer disease	2 (3)	2 (3)
Peripheral vascular disease	3 (4)	2 (3)
Primary malignancy, n (%)		
Lung cancer	28 (38)	33 (43)
Bronchogenic–adenocarcinoma	21 (29)	24 (32)
Bronchogenic–large cell	1 (1)	0 (0)
Bronchogenic–small cell	4 (5)	3 (4)
Bronchogenic–squamous	1 (1)	4 (5)
Bronchogenic–non-small-cell	0 (0)	1 (1)
Bronchogenic–other	1 (1)	1 (1)
Breast	20 (27)	20 (26)
Esophageal	2 (3)	1 (1)
Ovarian	3 (4)	6 (8)
Pancreatic	0 (0)	1 (1)
Renal	4 (5)	2 (3)
Other	15 (21)	11 (14)
Unknown	1 (1)	1 (1)
Pleural fluid lactate dehydrogenase, U/L, mean (SE)	592.7 (99.6)	577.6 (70.9)
Pleural fluid glucose, mg/d, mean (SE)	106.4 (5.9)	90.8 (5.6)
Pleural fluid protein, g/dl, mean (SE)	3.7 (0.1)	4.1 (0.1)
Pleural fluid pH, mean (SE)	7.5 (0)	7.4 (0)
Pleural fluid lymphocyte percentage, mean (SE)	43.5 (3.6)	36.9 (3.6)
Number of thoracenteses in last 12 mo, mean (SE)	1.8 (0.1)	1.6 (0.1)
Previous chemotherapy, n (%)	53 (73)	53 (70)
Previous radiation, n (%)	31 (42)	28 (37)
Pleural effusion location, n (%)		
Bilateral	13 (18)	3 (4)
Left	23 (32)	29 (38)
Right	37 (51)	44 (58)
Pleural effusion planned placement, n (%)		
Left	24 (33)	30 (39)
Right	49 (67)	46 (61)
Pleural cytology, n (%)		
Yes	60 (82)	59 (78)
Pleural biopsy, n (%)		
Yes	7 (10)	16 (21)

quantity of less than or equal to 50 ml of pleural fluid on three consecutive drainages and visible pleural fluid on CXR (radiographic score of 2–5) were brought to the hospital's procedure room and underwent an attempt at restoring catheter flow. This was first performed by flushing with 30 cc of sterile saline; in the event that simple flushing was not successful, then 2 mg of alteplase (Genentech, Inc., South San Francisco, CA) mixed with 8 cc of sterile saline was instilled in the catheter and allowed to dwell for 30 minutes. If flow was restored at this time, patients were instructed to return to their drainage schedule. However, if flow was not restored and the patient was not symptomatic, the catheter was removed with classification of the patient as PR. If symptoms were persistent, the patient was allowed to proceed to further management as per the primary provider's discretion.

Secondary End Points

The secondary end points were TTAP in days (from date of placement of the IPC to the date of first drainage of 50 ml of pleural fluid on three consecutive drainages), KPS score, the nine scales of the RAND Medical Outcome Study 36-Item Short Form Health Survey (SF-36), satisfaction of patients and caregivers with the IPC (using a questionnaire constructed for this study), and AEs. KPS and SF-36 were administered immediately before catheter placement and at 2, 6, and 12 weeks after placement. The satisfaction questionnaire was administered at 2, 6, and 12 weeks after placement.

Patients were provided with a diary and instructed to record the frequency of catheter drainage, volume and appearance of all pleural fluid recovered, pain associated with each pleural fluid drainage, and any AEs.

Another secondary end point was the agreement of the blinded reviewer and the treating physician in regards to scoring the CXR. The scores of any given CXR were judged to be in agreement if they were within 1 point of each other on the 5-point scale described previously.

Statistical Methods

To address the primary objective, the arm difference in proportion of patients achieving a CR + PR at 12 weeks post-procedure was tested with the chi-square test of proportions using a one-sided alpha of 0.025. A sample size of 68 patients per arm was chosen to allow the test 85% power to detect a difference in CR + PR rates of 0.30 versus 0.55 in the standard and aggressive arms, respectively. Given that it was expected that about 10% of the patients in each arm would be unevaluable, the final sample size was inflated to 75 patients per arm. The trial was stopped when the target number in each arm was reached.

TTAP was defined as the days from procedure to autopleurodesis; patients who died or could not complete the study without autopleurodesis were censored at the date of death or last follow-up, respectively. Patients without autopleurodesis by 12 weeks post-procedure were censored at 12 weeks. TTAP was compared between arms using the log-rank test and a cumulative incidence plot. Agreement in the CXR scores between the treating physician and the blinded reader was estimated as the proportion of scores within 1 point of each other. Descriptive statistics were used to report arm differences in the subscales of the SF-36, KPS score, patient satisfaction items, and AEs. A one-sided significance level of 0.025 was used for all three statistical tests. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Table 2. Clinical Response

Variable	Study Arm		Difference in Proportions (95% CI)*	Chi-Square *P* Value
	Aggressive (*n* = 73)	Standard (*n* = 76)		
Complete or partial response, n (%)	34 (47)	18 (24)	0.23 (0.08–0.38)	0.003
Complete response, n (%)	22 (30)	12 (16)	0.14 (0.01–0.28)	0.037
Final outcome, n (%)				
Complete response	22 (30)	12 (16)		
Partial response	12 (16)	6 (8)		
No response by end of study (12 wk)	12 (16)	10 (13)		
Inability to complete study (12 wk)	9 (12)	22 (29)		
Death before end of study (12 wk)	18 (25)	26 (34)		

Definition of abbreviation: CI = confidence interval.
*Difference is calculated as aggressive − standard.

Results

Patients

A total of 162 patients were enrolled and randomized with equal allocation to the two

Table 3. Reasons for Patients' Inability to Complete Study

Reason for Inability to Complete Study	Study Arm	
	Aggressive (*n* = 73)	Standard (*n* = 76)
All, n (%)	9 (12)	22 (29)
Patient factors, n (%)		
Disease progression/hospice	2 (3)	5 (7)
Draining more frequently than instructed	0 (0)	3 (4)
Draining less frequently than instructed	1 (1)	2 (3)
Inability to manage catheter at home	1 (1)	0 (0)
Inability to present to follow-up visits	1 (1)	2 (3)
Patient or family wishes	0 (0)	2 (3)
Catheter or disease factors, n (%)		
Pneumothorax	1 (1)	0 (0)
Trapped lung	1 (1)	0 (0)
Development of loculations	0 (0)	2 (3)
Chronic pain	1 (1)	2 (3)
Failed function of catheter (occlusion)	1 (1)	2 (3)
Accidental dislodgment	0 (0)	1 (1)
Infection	0 (0)	1 (1)

study arms. Thirteen of these patients were deemed screen failures because of exclusion criteria or patient factors discovered immediately after procedure performance (discovery of loculated effusion or trapped lung; effusion not meeting criteria for inclusion; prior attempted pleurodesis; patient or family choosing to leave study or to cease treatment in favor of hospice care; or, in the case of one patient, erroneous removal of the patient from the trial). A total of 149 patients were evaluable and were included in the primary analysis with 73 in the aggressive arm and 76 in the standard arm. The basic demographic and clinical characteristics of the patients and the chemical profiles of the pleural effusions were similar between the arms (Table 1).

Primary End Point

Patients in the aggressive drainage arm achieved autopleurodesis at a higher rate compared with the standard drainage arm (Table 2). This difference held true for the CR + PR rate (0.47 vs. 0.24; $P = 0.003$) and for the CR rate (0.30 vs. 0.16; $P = 0.037$). The CR + PR rate is the more clinically relevant of these end points, because the main objective of pleurodesis is the resolution of the patient's symptoms regardless of the appearance of the radiographs.

Compliance of patients with the drainage frequency per arm assignment, captured via the patient's diary, was 0.99 in the aggressive arm and 0.93 in the standard arm (difference of 0.052 with 95% confidence interval [CI], −0.01 to 0.12).

A total of 25% of patients in the aggressive arm and 34% in the standard arm died before achieving autopleurodesis by the end of the study (at 12 wk); 12% and 29% of patients in these two arms, respectively, were unable to complete the study. Table 3 summarizes causes for patients' inability to complete the study by arm. The rates of death and inability to complete study were anticipated because of the known medical complexity and short survival of patients diagnosed with malignant pleural effusion.

Secondary End Points

TTAP was shorter for patients in the aggressive arm than for patients in the standard arm ($P = 0.005$) (Figure 1). Median TTAP was 54 days (95% CI, 34–83) and 90 days (95% CI, 70 to nonestimable) for the aggressive and standard arms, respectively.

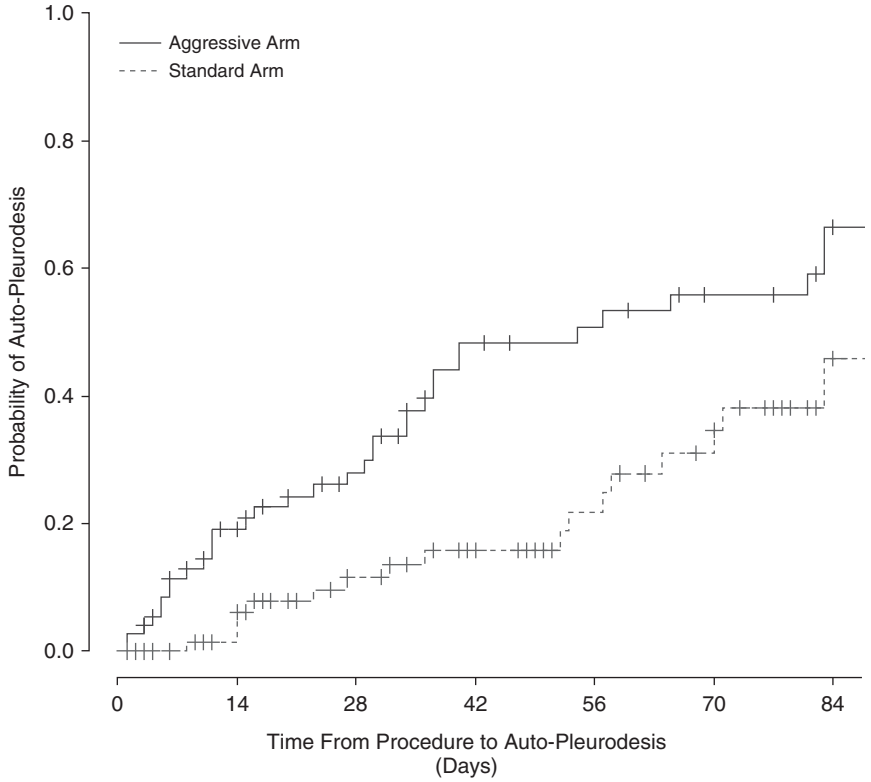

Figure 1. Probability of autopleurodesis and time to autopleurodesis based on study arm.

The KPS score (Table 4) and the SF-36 score were similar between arms at preinsertion, 2 weeks, and 12 weeks postinsertion (Table 5). The AE rates of the arms were similar; pain with drainage was the most common AE (Table 6). The arm difference in proportion of patients with at least one AE was 0.06 (95% CI, −0.22 to 0.10).

A high level of agreement in CXRs scores was found between the treating physicians and the independent blinded reviewer (Table 7).

Patients rated their satisfaction with the catheter in such areas as improvement of symptoms, education on proper use, ease of use at home, and willingness to choose the catheter again as a treatment option for dyspnea related to the pleural effusion. Patients in both arms showed a high overall satisfaction with the IPC (*see* Appendix E1 in the online supplement). At 2 weeks, the proportion of patients with relief of shortness of breath was 0.65 and 0.40 in the aggressive and standard arms, respectively (difference of 0.25 with 95% CI, 0.05–0.43). The proportion of patients willing to have the catheter again was 0.88 and 0.75, respectively (difference of 0.13 with 95% CI, −0.07 to 0.32).

Table 4. Karnofsky Performance Status Scores

Variable	Time Point	Study Arm		Difference in Means (95% CI)	*P* Value
		Aggressive	Standard		
KPS, mean (SE)	Preinsertion	65.9 (1.8)	63.5 (1.7)	2.4 (−2.5 to 7.4)	0.33
	2 wk	70 (2.4)	65 (2.4)	5 (−1.7 to 11.7)	0.15
	12 wk	80.4 (4.8)	71.8 (5.2)	8.5 (−6.2 to 23.3)	0.24

Definition of abbreviations: CI = confidence interval; KPS = Karnofsky Performance Status.
Sample sizes are n = 71 and n = 75 for aggressive and standard arms, respectively, for preinsertion; n = 59 and n = 58 for 2 wk; and n = 14 and n = 11 for 12 wk.
Difference is calculated as aggressive − standard.

Table 5. RAND MOS SF-36 Survey

Variable	Time Point	Study Arm		Difference in Mean (95% CI)
		Aggressive	Standard	
Health Change Score, mean (SE)	Preinsertion	19.8 (2.9)	18.4 (2.5)	1.4 (−6.2 to 9)
	2 wk	19.1 (3.2)	14.2 (2.8)	4.9 (−3.6 to 13.5)
	12 wk	18.3 (6.7)	33.3 (10.8)	−15 (−40.1 to 10.1)
Physical Functioning Score, mean (SE)	Preinsertion	28.4 (2.9)	29.9 (3)	−1.5 (−9.9 to 6.9)
	2 wk	31.3 (3.4)	31.5 (3.3)	−0.2 (−9.6 to 9.2)
	12 wk	39.3 (8.2)	38.3 (8.1)	1 (−23.1 to 25.1)
Role Limitations–Physical Health Score, mean (SE)	Preinsertion	9.6 (2.8)	6.3 (2.1)	3.3 (−3.6 to 10.3)
	2 wk	15.9 (4)	9.7 (3.3)	6.2 (−4.2 to 16.6)
	12 wk	23.3 (9.9)	18.8 (11.1)	4.6 (−26.1 to 35.3)
Role Limitations–Emotional Problems Score, mean (SE)	Preinsertion	45.7 (5.3)	38.9 (5.3)	6.8 (−8 to 21.6)
	2 wk	49.1 (6.3)	51.2 (6.2)	−2.1 (−19.8 to 15.5)
	12 wk	55.6 (12.9)	52.8 (12.6)	2.8 (−34.9 to 40.5)
Energy/Fatigue Score, mean (SE)	Preinsertion	33.2 (2.3)	27 (2.3)	6.2 (−0.3 to 12.6)
	2 wk	33.8 (3)	28.4 (3)	5.4 (−3 to 13.8)
	12 wk	41.4 (5.7)	35.8 (7.5)	5.6 (−13.5 to 24.7)
Emotional Well-Being Score, mean (SE)	Preinsertion	65.2 (2.8)	58.8 (2.7)	6.3 (−1.5 to 14.1)
	2 wk	70.4 (2.5)	63.7 (3.1)	6.7 (−1.2 to 14.6)
	12 wk	76.9 (5.1)	70.7 (9.1)	6.2 (−14.6 to 27)
Social Functioning Score, mean (SE)	Preinsertion	46.9 (3.7)	44.3 (3.5)	2.6 (−7.5 to 12.7)
	2 wk	50.2 (3.8)	49.3 (4)	0.9 (−10 to 11.8)
	12 wk	65.8 (7.3)	62.5 (9.2)	3.3 (−20.5 to 27.2)
Pain Score, mean (SE)	Preinsertion	54.1 (3.4)	47.5 (3.5)	6.6 (−3 to 16.3)
	2 wk	57 (3.8)	54.6 (4)	2.4 (−8.6 to 13.4)
	12 wk	62.8 (5.8)	58.5 (8.1)	4.3 (−15.6 to 24.2)
General Health Score, mean (SE)	Preinsertion	39.7 (2.3)	33.3 (2.2)	6.4 (0 to 12.7)
	2 wk	40.8 (3)	33.8 (3.2)	7 (−1.6 to 15.6)
	12 wk	38.7 (4.6)	51.3 (7)	−12.6 (−29.3 to 4.1)

Definition of abbreviations: CI = confidence interval; RAND MOS SF-36 = RAND Medical Outcome Study 36-Item Short Form Health Survey.
All areas have possible score range of 0 to 100, where higher scores are associated with more favorable health states.
Difference is calculated as aggressive − standard. Sample sizes are n = 73 and n = 72 for aggressive and standard arm, respectively; for preinsertion, n = 55 and n = 54 for 2 wk; and n = 15 and n = 12 for 12 wk.

From a socioeconomic perspective, most catheter supplies were delivered to the patients' homes by mail within 1 to 5 days, catheters were drained by a family member at home, and supplies were covered by insurance either completely or with a copay. Only a small proportion of patients believed that the catheters posed a financial burden.

Table 6. Adverse Events

Variable	Study Arm		Difference in Proportions (95% CI)
	Aggressive (*n* = 73)	Standard (*n* = 76)	
Patients who had at least one adverse event, n (%)	38 (52)	44 (58)	−0.06 (−0.22 to 0.10)
Patients with complications, n (%)			
Pain with drainages	25 (34)	29 (38)	−0.04 (−0.19 to 0.12)
Catheter occlusion	8 (11)	4 (5)	0.06 (−0.03 to 0.14)
Catheter dislodgement	1 (1)	1 (1)	0.0 (−0.04 to 0.04)
Catheter misplacement	0 (0)	1 (1)	−0.01 (−0.04 to 0.01)
Other, related to catheter*	8 (11)	6 (8)	0.03 (−0.06 to 0.12)
Other, unrelated to catheter*	18 (25)	17 (22)	0.02 (−0.11 to 0.16)
Infection rate, n (%)			
Any	3 (4)	1 (1)	0.03 (−0.02 to 0.08)
Cellulitis	2 (3)	0 (0)	0.03 (−0.01 to 0.06)
Empyema	0 (0)	1 (1)	−0.01 (−0.04 to 0.01)
Other, infected vascular access	1 (1)	0 (0)	0.01 (−0.01 to 0.04)

Definition of abbreviation: CI = confidence interval.
**See* Appendix E2 for list of other adverse events related or unrelated to the catheter.

Discussion

Our trial has shown that a more aggressive daily drainage of pleural fluid via the IPC is superior to the standard every other day drainage strategy in patients with malignant pleural effusions. The aggressive drainage led to a higher rate of autopleurodesis and a more rapid autopleurodesis. The autopleurodesis rate observed in the conservative drainage arm of our study (24%) was lower than previously reported in other trials, which had used every other day or less frequent drainage schedule (42.9–51%) (3, 12, 14). This could be explained by the shorter follow-up period of our study (12 wk) as opposed to follow-up until catheter removal or death in other studies. Our decision to choose the 12-week follow-up period was predicated on the average survival of patients with malignant pleural effusions and the knowledge that autopleurodesis is less likely to occur past the 12-week postinsertion time point.

We defined partial pleurodesis as a decline in the quantity of pleural fluid to less

Table 7. Proportion of CXR Scores, Measured by the Treating Physician and Blinded Reviewer, within One Point on the Scoring Scale

Time Point	N	Proportion (95% CI)
Preinsertion	136	0.98 (0.94–1.00)
Procedure day	131	0.92 (0.85–0.96)
2 wk	101	0.94 (0.88–0.98)
6 wk	52	0.96 (0.87–1.00)
12 wk	22	1.00 (0.85–1.00)

Definition of abbreviations: CI = confidence interval; CXR = chest radiograph.

than or equal to 50 ml on three consecutive attempted drainages, radiographic scores of 2–5, and lack of symptoms (shortness of breath, cough, or chest pain). None of our study subjects who achieved PR had a radiographic score of 5; only one patient had a score of 4 and the rest had a score of 3 or less.

The mortality rate in our study was higher than expected despite the investigators following the study protocol in excluding patients with projected life expectancy less than or equal to 30 days as predicted by KPS score of less than 30. A study by Burrows and coworkers (15) of 85 patients with malignant pleural effusions showed a median survival of 395 days when the KPS score is greater than or equal to 70, as opposed to a median survival of 34 days with a KPS score of less than or equal to 30. The average KPS score in our study was greater than 60 in both arms. Our inexact prediction likely signals the heterogeneous nature of malignant pleural effusion and the inherent imprecision in relying on clinical factors or weakly validated assessment tools. The rate of patients' inability to complete the study to 12 weeks in both arms was expected and reflected the deteriorating health of the advanced cancer patient.

The AE rate of IPCs was acceptable with no difference between the two arms. Chest pain during drainage is relatively common and usually managed by slowing or terminating fluid withdrawal. Only three patients had to leave the study because of chronic pain associated with the catheter. The infection rate was low in our study (<3% overall) and was not higher in the aggressive drainage arm as may be feared because of more frequent accessing and maneuvering of the pleural catheter. A recent large international multicenter study found an infection rate of 4.9% associated with the IPC with a median time to infection of 62 days (interquartile range, 39–177) after catheter insertion (16).

Our study was not blinded to patients or investigators but we attempted to detect bias by assessing the level of agreement in CXRs scores (on a scale from 0 to 5) between the treating physician and an independent blinded review. CXR scores were an integral part in classifying the primary outcome of autopleurodesis and were found to be similar (>92% agreement in scores at all assessment points of the study).

Patients' scores on both the SF-36 survey and KPS were similar between the two arms. This likely reflects the positive perceived impact of the IPC on quality of life regardless of drainage frequency.

With the widespread use of IPC as an outpatient treatment option for malignant pleural effusion, there is some concern that the burden of care has been shifted to the patients and their families and potential hardship at home has been imposed. Our study surveyed patients and their caregivers and found a high level of satisfaction with management of catheters at home and willingness to choose this treatment option again. This likely reflects a well-known desire for even terminal patients to maintain a degree of autonomy that is inherent in the self-management of the IPC.

Prior cost analyses have compared the cost-effectiveness of the IPC with talc pleurodesis in patients with malignant pleural effusions and found them to be either less costly or have similar to slightly higher costs but with a definitive advantage of the IPC when survival is short (6–14 wk) (17–19). Our study did not address the cost of care and it is not known at this time if the shorter time to pleurodesis may offset the cost of using drainage bottles on a daily basis in the aggressive approach. There may also be an additional cost when the home drainage is performed by a visiting nurse; however, most patients in our study either drained themselves or relied on a family member to do so. Ultimately, the benefits of dyspnea relief and freedom from catheter may outweigh the potential increase in cost.

In conclusion, daily drainage of the IPC in patients with malignant pleural effusions, as compared with every other day drainage, led to more frequent and rapid autopleurodesis. Quality of life and AEs were similar with either approach. Our findings should inform the choice of clinicians and patients on drainage frequency and weigh into a customized approach that incorporates consideration of efficacy, social support, and available resources. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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