Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion
The AMPLE Randomized Clinical Trial

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🞣 Supplemental content

IMPORTANCE Indwelling pleural catheter and talc pleurodesis are established treatments for malignant pleural effusions among patients with poor prognosis.

OBJECTIVE To determine whether indwelling pleural catheters are more effective than talc pleurodesis in reducing total hospitalization days in the remaining lifespan of patients with malignant pleural effusion.

DESIGN, SETTING, AND PARTICIPANTS This open-label, randomized clinical trial included participants recruited from 9 centers in Australia, New Zealand, Singapore, and Hong Kong between July 2012 and October 2014; they were followed up for 12 months (study end date: October 16, 2015). Patients (n = 146) with symptomatic malignant pleural effusion who had not undergone indwelling pleural catheter or pleurodesis treatment were included.

INTERVENTIONS Participants were randomized (1:1) to indwelling pleural catheter (n = 74) or talc pleurodesis (n = 72), minimized by malignancy (mesothelioma vs others) and trapped lung (vs not), and stratified by region (Australia vs Asia).

MAIN OUTCOMES AND MEASURES The primary end point was the total number of days spent in hospital from procedure to death or to 12 months. Secondary outcomes included further pleural interventions, patient-reported breathlessness, quality-of-life measures, and adverse events.

RESULTS Among 146 randomized patients (median age, 70.5 years; 56.2% male), 2 were excluded. The indwelling pleural catheter group spent significantly fewer days in hospital than the pleurodesis group. The reduction was mainly in effusion-related hospitalization days. Fewer patients randomized to indwelling pleural catheter required further ipsilateral invasive pleural drainages. There were no significant between-group differences in improvements in breathlessness or quality of life. Adverse events occurred in both groups: 30 events in 22 catheter patients and 23 events in 13 talc pleurodesis patients.

	Indwelling Pleural Catheter (n = 73)	Talc Pleurodesis (n = 71)	Estimated Difference in Location or Proportions (95% CI)	P Value
Primary Outcome				
Total all-cause hospital stay, median (IQR), d	10 (3-17)	12 (7-21)	2.92 (0.43-5.84)	.03
Secondary Outcomes				
Effusion-related hospital stay, median (IQR), d	1 (1-3)	4 (3-6)	2.06 (1.53-2.58)	<.001
Further ipsilateral invasive pleural procedures required, No. (%)	3 (4)	16 (22)	0.18 (0.08-0.29)	.001

CONCLUSIONS AND RELEVANCE Among patients with malignant pleural effusion, treatment with an indwelling pleural catheter vs talc pleurodesis resulted in fewer hospitalization days from treatment to death, but the magnitude of the difference is of uncertain clinical importance. These findings may help inform patient choice of management for pleural effusion.

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Malignant pleural effusion can complicate most cancers.[1,2] The resultant breathlessness is often distressing and impairs quality of life (QoL). Drainage of the effusion can relieve symptoms but requires hospital attendance and invasive pleural procedures.

Malignant pleural effusions herald advanced cancers and often limited life expectancies.[3] The aims of management are to provide effective symptom relief with minimal interventions and hospitalization. Freedom from hospital admissions is an important goal for patients and families.[4]

Talc pleurodesis and drainage with indwelling pleural catheters are 2 established approaches for symptomatic malignant pleural effusions.[5] To our knowledge, no studies have directly compared their effect on the total time patients with malignant pleural effusion spent in hospital: a significant end point to patients and the health care system.

Talc pleurodesis requires an initial hospitalization of several days and failed in approximately 30% of patients within 3 months in 2 randomized clinical trials (RCTs),[6,7] which may necessitate further hospitalizations for fluid management. Indwelling pleural catheters offer an alternative to pleurodesis. They can be inserted during a short-stay procedure to allow ambulatory drainage[8] and, like pleurodesis, provide improvement in breathlessness and QoL.[9,10] However, indwelling pleural catheter treatment requires ongoing care, with potential complications that trigger hospital care (eg, pleural infection, blockage, symptomatic loculation, and catheter track metastasis).[11-13] A pilot nonrandomized study (n = 65) suggested that patients with malignant pleural effusion treated with indwelling pleural catheters spent less time in hospital (8% vs 11.2% of their remaining lifespan) than those treated with talc pleurodesis.[14]

The Australasian Malignant Pleural Effusion (AMPLE) trial was a multicenter, randomized, open-label study that compared the effects of indwelling pleural catheter and talc slurry pleurodesis on the total number of days patients with malignant pleural effusion spent in hospital.[15] Secondary end points assessed the need for further pleural interventions, effects on hospitalization directly related with pleural effusions, symptom improvements, survival, and adverse events.

Methods

This trial was conducted at 9 centers: Sir Charles Gairdner, Fiona Stanley, Swan District, Princess Alexandra, and St George & Sutherland hospitals in Australia; Wellington and Middlemore hospitals in New Zealand; National University Hospital Singapore; and Queen Mary Hospital Hong Kong. Ethics and governance approvals were obtained from the human research ethics committee at all sites, the primary committee being the Sir Charles Gairdner Group Human Research and Ethics Committee. Written informed consent was obtained from each study participant. The full trial protocol is available in Supplement 1.

All patients enrolled were adults with malignant pleural effusions with histocytological confirmation of pleural malignancy or recurrent exudative pleural effusions with no alter-

Key Points

Question Is management of malignant pleural effusion with indwelling pleural catheter more effective than talc pleurodesis in minimizing hospitalization in patients' remaining lifetime?

Findings In this randomized clinical trial of 146 patients with malignant pleural effusion, treatment with indwelling pleural catheter compared with talc pleurodesis significantly reduced lifetime hospitalization days (median, 10 vs 12 days).

Meaning Among patients with malignant pleural effusion, treatment with an indwelling pleural catheter resulted in fewer hospitalization days from treatment to death, but the difference is of uncertain clinical importance.

native cause in the setting of histocytologically proven extrapleural cancer. Exclusion criteria included age younger than 18 years, effusion less than 2 cm at maximum depth on imaging, expected survival of less than 3 months, chylothorax, previous lobectomy or pneumonectomy on the side of effusion, previous attempted pleurodesis, pleural infection, hypercapnic ventilatory failure, blood leukocyte count less than 1000/μL (to convert to ×10⁹ per liter, multiply by 0.001), pregnant or lactating women, irreversible bleeding diathesis, and visual impairment.

Randomization

Participants were randomized 1:1 to either indwelling pleural catheter or talc slurry pleurodesis. Allocation concealment was maintained through randomization by computer in real time (Filemaker Server; Filemaker Inc). Once baseline clinical data were entered, treatment was allocated with a probability of 0.5 to 0.8 to the treatment group to maintain between-group balance on the key prognostic factors (mesothelioma vs nonmesothelioma; known trapped lung or not), and stratified between Australasian (Australia/New Zealand) vs Asian (Singapore/Hong Kong) sites to account for potential differences in median survival of different cancer types, pleurodesis failure rate, and ethnicity.[2,16] Patients with previous evidence of incomplete lung expansion after drainage were defined as having a trapped lung.

Interventions

Patients randomized to the indwelling pleural catheter group had the catheter inserted as per the modified Seldinger technique with tunneling, followed by fluid removal, as a same-day or overnight-stay procedure unless there were other medical reasons necessitating continual hospitalization. Ambulatory fluid drainages were performed as guided by symptoms of individual patients by caregivers or nurses using either vacuum bottles or drainage bags. Indwelling pleural catheters were removed when clinically indicated, most commonly because of cessation of fluid accumulation. Participants randomized to talc pleurodesis underwent tube thoracostomy (12-18F), followed by instillation of talc slurry as per routine practice of the recruiting hospital. All participants received usual standard care including chemotherapy, radiotherapy, and palliative care as recommended by their attending clinicians.

Outcomes

Primary Outcome

The primary outcome was the total number of days spent in hospital from trial intervention to death or up to the 12-month follow-up visit. Any hospital, including hospice, admission involving 1 or more days was included. One day referred to a hospital stay crossing midnight. Day-case procedures (eg, chemotherapy) were excluded. The duration of hospital admissions was decided independently by the treating physicians. Data on all hospital admissions were collected from participants (during follow-up visits), caregivers, general practitioners, electronic databases, and case records. An independent assessor (C.K.) reviewed the validity (justification and duration) of each hospital admission based on the discharge summary and full hospital record (if needed).

Secondary Outcomes

Secondary outcomes included the following: first, the total number of days and episodes of hospitalization from pleural effusion–related causes, including admissions for management of pleural effusion, associated symptoms, related procedures, and/or their complications. Second, the need for further pleural drainage procedures. Third, breathlessness as measured using a visual analog scale (VAS) validated for patients with malignant pleural effusion.[17] The VAS was a 100-mm line anchored with "no breathlessness" at 100 mm and "worst imaginable breathlessness" at 0 mm. Participants recorded their VAS scores daily in the initial 14 days and at follow-up visits at 1, 3, 6, 9, and 12 months. If patients were unable to attend follow-up, a research nurse (C.A.R.) would record the patient's reported score by telephone. Fourth, QoL as quantified by (1) a modified EuroQol 5 Dimensions (EQ5D) questionnaire score[18] for QoL and (2) a 100-mm VAS recorded at baseline (for both) and 8 and 14 days (for EQ5D) or daily for 14 days (for VAS) and 1, 3, 6, 9, and 12 months (for both). Fifth was survival and sixth was adverse and serious adverse events.

Statistical Analyses

The study was powered to detect a difference of 5 days or more spent in hospital between the groups (80% power; α = .05). There is no established minimal clinically important difference for this end point. A difference of 5 days was determined by consensus among the investigators based in part on a previous nonrandomized study that found a difference of (median) 11.5 days in patients treated with indwelling pleural catheter over those treated with talc pleurodesis.[14] An estimated 65 participants were needed per group, based on a total stay of 18 days and an SD of 9.3 days in the pleurodesis group from this study.[14] The recruitment target of 146 allowed for a lost-to-follow-up rate of 12%.

Two-sided superiority analyses were conducted on an intention-to-treat basis for all outcomes. The primary end point was analyzed initially using a Mann-Whitney U test; the Hodges-Lehmann (HL) estimate of location shift between the groups and corresponding 95% CI is also presented. Subsequent supporting analyses were carried out using a negative binomial model with adjustments for actual length

Figure 1. Participant Enrollment, Treatment, Follow-up, and Analysis
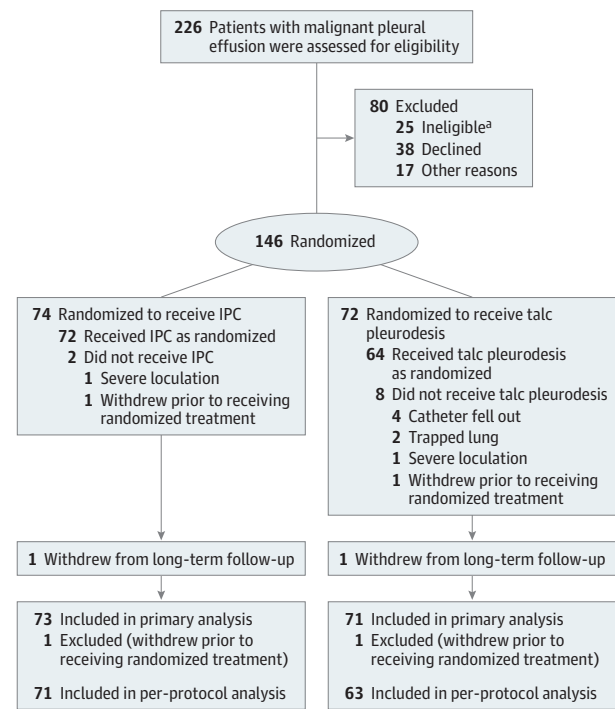
IPC indicates indwelling pleural catheter.

[a] A total of 25 patients were screened but found ineligible for the following reasons: expected survival less than 3 months (n = 5), inability to care for IPC for logistic reasons (remote location) (n = 4), previous pleurodesis (n = 6), nonmalignant etiology (n = 7), and asymptomatic from effusion (n = 3).

of follow-up (accounting for death and withdrawals), minimization variables, and random effect of center. The total effusion-related and non–effusion-related hospital bed days were similarly analyzed. The number of days spent in hospital, expressed as a percentage of the patients' total days in the trial (from procedure to death or the 12-month follow-up), and the number of days in hospital for initial/subsequent hospitalizations, were compared using Mann-Whitney U tests as post-hoc analyses, with HL estimates of location shift between the groups and corresponding 95% CIs presented. Further post-hoc subgroup analyses by cancer type and by first or subsequent hospitalizations were separately performed using the same method described for the full group analyses.

VAS and EQ5D scores were analyzed using linear mixed effects models, including fixed effects of treatment, time and time-dependent covariates as appropriate, and random effects of individual and center, with adjustments made for minimization variables as appropriate. Where missing data were present in the VAS and EQ5D outcomes, subsequent sensitivity analyses were carried out using multiple imputation.

χ^2 Tests were used to compare the proportions of deaths in the trial with differences in proportions and 95% CIs presented. Time to death was analyzed using both log-rank test and Cox proportional hazards models, the latter adjusting for

Table 1. Baseline Demographic Data for 146 Randomized Patients With Malignant Pleural Effusion

Characteristic	Indwelling Pleural Catheter (n = 74)	Talc Pleurodesis (n = 72)
Age, median (range), y	71.0 (38-92)	70.5 (43-90)
Male, No. (%)	39 (53)	43 (60)
Side of intervention: right, No. (%)[a]	44 (59)	38 (53)
Type of primary malignancy, No. (%)		
Mesothelioma	20 (27)	18 (25)
Nonmesothelioma		
Lung	19 (26)	29 (40)
Breast	14 (19)	4 (6)
Others	21 (28)	21 (29)
Known trapped lung, before randomization, No. (%)[b]	2 (3)	3 (4)
ECOG score, No. (%)[c]		
0-2	53 (72)	53 (74)
3-4	19 (26)	14 (19)
Unknown	2 (3)	5 (17)
Effusion size grade, No. (%)[d]		
Small (0-1)	0	0
Moderate (2-3)	38 (51)	38 (53)
Large (4-5)	36 (49)	34 (47)
VAS dyspnea score, mean (SD), mm[e]	48.4 (27.0)	50.2 (26.0)
VAS QoL score, mean (SD), mm[f]	51.6 (26.1)	55.9 (25.1)
EQ5D QoL score, mean (SD)[g]	31.3 (10.5)	32.6 (9.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EQ5D, EuroQol 5 Dimensions; QoL, quality-of-life; VAS, visual analog scale.

[a] Patients subsequently requiring contralateral procedures were treated according to the treating clinician and complications were reported in the trial only if they occurred on the trial intervention side and/or were attributable to the trial intervention.

[b] Defined as incomplete ipsilateral lung expansion on imaging after pleural drainage.

[c] ECOG performance status score runs from 0 to 5, where 0 is fully active, 1 is restricted in physical strenuous activity, 2 is unable to carry out any work activities, 3 is only able to carry out limited self-care activities, 4 is completely disabled, and 5 is dead.

[d] Baseline effusion size was graded on chest radiograph immediately prior to trial intervention, using a validated grading system whereby grade 0 referred to no radiographic evidence of pleural fluid; grade 1, blunting of the costophrenic angle; grade 2 to 5, fluid occupying less than 25%, 25% to 50%, 51% to 75%, and more than 75% of the hemithorax, respectively.[20] This scale has previously been used to predict pleurodesis and indwelling pleural catheter use in patients with a malignant pleural effusion.[21]

[e] The VAS was a 100-mm line anchored with "no breathlessness" at 100 mm and "worst imaginable breathlessness" at 0 mm.

[f] QoL was measured using a VAS; the VAS was a 100-mm line anchored with "best QoL" at 100 mm and "worst QoL" at 0 mm.

[g] EQ5D QoL score consisted of 5 domains: mobility, self-care, usual activities, discomfort/pain, and anxiety/depression. Each domain was graded by the patient from 0 (worst imaginable) to 10 (best imaginable) and the total score out of a maximum 50 points was recorded.

minimization variables, with hazard ratios and 95% CIs presented. Frequencies of serious adverse events and further pleural intervention were described. The latter were analyzed with the Fisher exact test and differences in proportions and 95% CIs presented. No adjustment was made for multiple comparisons and thus the secondary outcomes should be

considered exploratory, yielding hypothesis-generating findings. For all analyses, statistical significance was set at .05 and 2-sided tests were performed. All analyses were carried out using the R environment for statistical computing (R Foundation for Statistical Computing).[19]

Results

Patients with a malignant pleural effusion (n = 146; 56.2% male) were recruited between July 2012 and October 2014 (**Figure 1**). The median age was 70.5 years (range, 38-92) and the most common underlying malignancies were lung cancer (n = 48), mesothelioma (n = 38), and breast carcinoma (n = 18). Both groups were well matched in their demographics, ratio of primary vs secondary pleural malignancies, effusion sizes, baseline symptom scores, and Eastern Cooperative Oncology Group status (**Table 1**). One patient from each group withdrew before presenting for the randomized intervention; they were excluded from all analyses.

Hence, 144 patients (73 in the indwelling pleural catheter group and 71 in the pleurodesis group) were included in the intention-to-treat analyses. Per-protocol analyses were performed in 134 patients, after excluding 12 patients (3 from the indwelling pleural catheter group and 9 from the pleurodesis group) who did not receive their full allocated treatment as stated in the protocol. There were 2 withdrawals and a further 10 that did not receive their randomized therapy for individual, mostly technical, reasons such as chest drain dislodged before talc instillation (Figure 1).
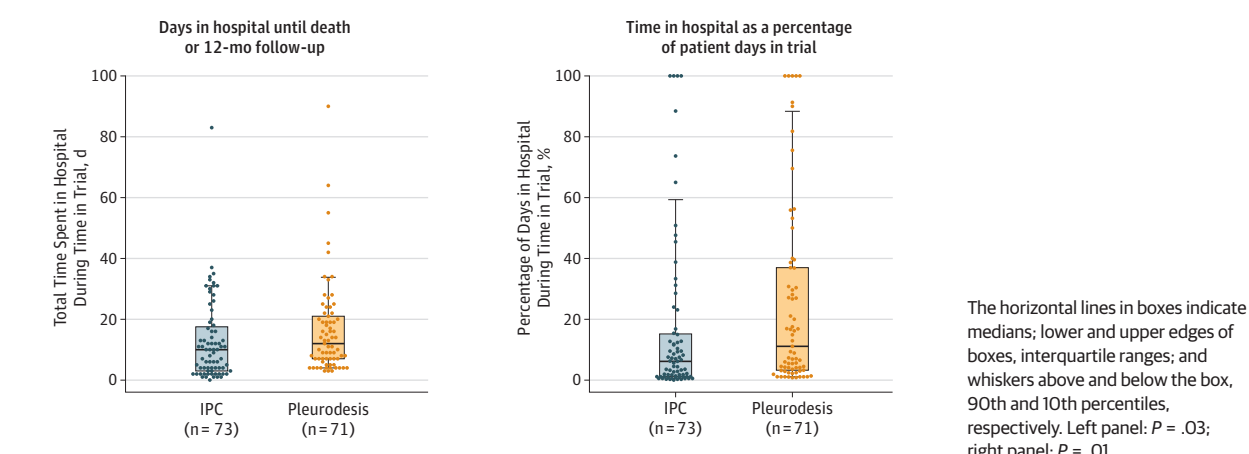
Primary End Point

Overall, patients with malignant pleural effusions spent a substantial number of days in hospital (median, 10.0 days; interquartile range [IQR], 4-19; mean [SD], 14.5 [14.4] days). This represented an important part of their total days in trial (median, 7.1% [IQR, 1.9%-28.3%]); mean [SD], 21.0 [29.0] %) (**Figure 2**).

There was a statistically significant difference in the total days spent in hospital among patients treated with indwelling pleural catheter compared with talc pleurodesis (median, 10 days [IQR, 3-17] vs 12 days [IQR, 7-21], respectively; P = .03; HL estimate, 2.92 days; 95% CI, 0.43-5.84) (**Table 2**). The mean reduction in hospitalization was 3.6 days per patient (mean [SD], 12.7 [13.4] in the indwelling pleural catheter group vs 16.3 [15.2] in the pleurodesis group).

These findings remained consistent in per-protocol analysis, which confirmed a significant reduction in total days spent in hospital using indwelling pleural catheter (median, 10 days [IQR, 3-17] vs 13 days [IQR, 7-22] in the pleurodesis group; P = .02; HL estimate, 3.38 days; 95% CI, 0.85-6.62). The mean reduction in hospitalization from per-protocol analysis was 4.5 days per patient (mean [SD], 12.6 [13.4] in the indwelling pleural catheter vs 17.1 [15.8] in the pleurodesis group). The differences in total hospitalization days remained consistent after adjustment for minimization variables and days in trial and fitting center as a random effect during intention-to-treat and per-protocol analyses (Table 2).

Figure 2. Time in Hospital Until Death or 12-Month Follow-up

The horizontal lines in boxes indicate medians; lower and upper edges of boxes, interquartile ranges; and whiskers above and below the box, 90th and 10th percentiles, respectively. Left panel: *P* = .03; right panel: *P* = .01.

Other End Points

Days Spent in Hospital for Pleural Effusion–Related Causes

Indwelling pleural catheter significantly reduced the number of total hospitalization days for causes directly related to pleural effusion and treatment complications (median, 1 day [IQR, 1-3] vs 4 days [IQR, 3-6] in the pleurodesis group; *P* < .001; HL estimate, 2.06 days; 95% CI, 1.53-2.58; Table 2), and remained significant when adjusted for minimization variables and days in trial (*P* < .001). The median (IQR) days in hospital for the initial admission (for indwelling pleural catheter insertion or pleurodesis) was shorter for the indwelling pleural catheter group than the pleurodesis group: 1 (1-2) vs 3 (3-4) days, respectively (*P* < .001; HL estimate, 2.09 days; 95% CI, 1.78-2.39). There was no significant difference in the subsequent number of effusion-related hospital days in the indwelling pleural catheter group until death (or 12-month follow-up) (median, 0 days [IQR, 0-1] vs 0 days [IQR, 0-0.5] for the talc group; *P* = .08; HL estimate, −0.18 days; 95% CI, −0.41 to 0.01).

Need for Further Pleural Drainage Procedures

Significantly fewer patients in the indwelling pleural catheter group (n = 3; 4.1%) required further pleural interventions for ipsilateral fluid drainage after the initial procedure (vs n = 16 in the pleurodesis group; 22.5%) (*P* = .001; difference in proportions, 0.18; 95% CI, 0.08-0.29).

Pleurodesis failure was diagnosed when a further ipsilateral pleural procedure was needed for symptom relief. Talc pleurodesis failed in 16 patients (22.5%) and required further drainage interventions after a median of 32 days (IQR, 15.5-72.5). Most patients with pleurodesis failure (n = 10) were subsequently successfully treated with indwelling pleural catheter. Others received repeated therapeutic drainages (n = 3) and repeat talc slurry pleurodesis (n = 2); the latter failed again in 1 patient who then had video-assisted thoracoscopic surgery with talc poudrage. One underwent thoracotomy with partial pleurectomy and a pericardial window to control recurrent pleural and pericardial fluids.

Three patients in the indwelling pleural catheter group required further pleural punctures. One had loculated effusion that prevented indwelling pleural catheter insertion and was treated with blunt dissection and large-bore chest drain insertion, followed by successful pleurodesis. One developed a pneumothorax with subcutaneous emphysema that required chest tube placement. The third patient had recurrence of effusion after successful removal of the initial indwelling pleural catheter and was treated with a second indwelling pleural catheter.

Indwelling pleural catheter was removed in 25 of 83 patients (30.1%) including those randomized to indwelling pleural catheter treatment (21/73 patients; 28.8%) and those who underwent indwelling pleural catheter insertion after failed pleurodesis (4/10 patients; 40%).

Breathlessness Scores

Baseline VAS scores showed that the patients were breathless (indwelling pleural catheter group: mean, 50.8 mm, 95% CI, 39.9-61.6; pleurodesis group: mean, 52.8 mm, 95% CI, 42.0-63.5). The symptoms were significantly improved by day 1 after the procedure, with improvements in VAS score of 14.5 mm (95% CI, 8.4-20.7) for the indwelling pleural catheter group and 17.4 mm (95% CI, 11.1-23.7) for the pleurodesis group. The improvements were maintained in subsequent visits up to 12 months. No significant differences were found in the magnitude of symptom benefits derived from indwelling pleural catheter treatment or pleurodesis (**Figure 3**A).

QoL

QoL measures quantified by VAS and by modified EQ5D both revealed a pattern similar to that of the breathlessness scores. The groups were balanced at their baseline QoL scores, which significantly increased from initial treatment with indwelling pleural catheter or pleurodesis. The improvement was maintained throughout the study follow-up in both groups. No significant differences were found in the magnitude of QoL improvement derived from indwelling pleural catheter treatment or pleurodesis (Figure 3B-C).

Survival

Within the follow-up period (median, 204 days), 60.3% (44/73) of the patients in the indwelling pleural catheter group and 71.8% (51/71) in the pleurodesis group died (difference in

Table 2. Summary of Primary and Secondary Outcomes by Intention-to-Treat Analysis

Outcome	Indwelling Pleural Catheter (n = 73)	Talc Pleurodesis (n = 71)	Estimated Difference (95% CI)[a]	P Value
Primary Outcome				
Total all-cause hospital stay duration, d				
Median (IQR)	10 (3-17)	12 (7-21)	2.92 (0.43 to 5.84)	.03
Mean (SD)[b]	12.7 (13.4)	16.3 (15.2)		
Secondary Outcomes				
Effusion-related hospital stay duration, d				
Median (IQR)	1 (1-3)	4 (3-6)	2.06 (1.53 to 2.58)	<.001
Mean (SD)[b]	3.1 (4.3)	4.7 (3.1)		
Non–effusion-related hospital stay duration, d				
Median (IQR)	5 (1-13)	7 (2-15)	0.92 (−1.10 to 3.73)	.37
Mean (SD)[b]	9.6 (12.7)	11.6 (14.7)		
VAS dyspnea scores, estimated mean (95% CI), mm				
Baseline	50.0 (37.2 to 62.7)	52.2 (39.3 to 63.1)	2.27 (−5.33 to 9.88)	.56
1 d after procedure	64.5 (51.4 to 75.5)	69.7 (56.5 to 82.9)	5.25 (−3.21 to 13.71)	.22
30 d after procedure	69.7 (56.7 to 82.6)	72.2 (59.0 to 85.5)	2.58 (−5.91 to 11.08)	.55
6 mo after procedure	71.1 (57.8 to 84.5)	71.2 (57.3 to 85.1)	0.03 (−9.89 to 9.96)	.99
12 mo after procedure	69.4 (55.4 to 83.4)	59.0 (44.6 to 73.4)	−10.42 (−21.90 to 1.06)	.07
VAS QoL scores, estimated mean (95% CI), mm				
Baseline	52.4 (43.4 to 61.4)	56.7 (47.5 to 65.9)	4.24 (−3.76 to 12.25)	.27
2 d after procedure	60.3 (50.9 to 69.7)	58.5 (48.9 to 68.1)	−1.75 (−10.65 to 7.14)	.74
30 d after procedure	61.5 (52.2 to 70.8)	67.3 (57.6 to 77.0)	5.79 (−3.11 to 14.69)	.17
6 mo after procedure	67.4 (57.6 to 77.3)	66.1 (55.5 to 76.7)	−1.27 (−11.64 to 9.09)	.89
12 mo after procedure	61.7 (50.9 to 72.4)	56.3 (45.0 to 67.6)	−5.34 (−17.30 to 6.62)	.43
EQ5D QoL scores, estimated mean (95% CI)				
Baseline	31.2 (26.7 to 35.7)	32.3 (27.8 to 36.8)	1.12 (−2.34 to 4.59)	.46
8 d after procedure	34.1 (29.5 to 38.7)	35.3 (30.6 to 40.0)	1.18 (−2.73 to 5.10)	.48
30 d after procedure	35.2 (30.6 to 39.8)	34.5 (29.8 to 39.2)	−0.67 (−4.59 to 3.23)	.86
6 mo after procedure	33.9 (29.1 to 38.7)	33.1 (28.0 to 38.1)	−0.84 (−5.34 to 3.66)	.84
12 mo after procedure	32.4 (27.3 to 37.5)	31.5 (26.2 to 36.8)	−0.92 (−6.07 to 4.22)	.83
Deaths at 12 mo, No. (%)	44 (60)	51 (72)	0.12 (−0.05 to 0.28)	.20
Further ipsilateral invasive pleural procedures required, No. (%)	3 (4)	16 (22)	0.18 (0.08 to 0.29)	.001

Abbreviations: EQ5D, EuroQol 5 Dimensions; IQR, interquartile range; QoL, quality of life; VAS, visual analog scale.

[a] Differences in VAS and EQ5D scores are differences in estimated means with 95% CIs and P values for the difference. Hodges-Lehmann location shift estimates and 95% CIs are presented for comparisons associated with differences in medians. Differences in proportions and 95% CIs for differences are provided for complications along with Fisher exact test P values.

[b] Data not normally distributed but mean (SD) included to enable future economic calculations in savings of days in population cohorts.

proportions, 0.12; 95% CI, −0.05 to 0.28; Table 2). When survival was analyzed as the time to death, no statistically significant differences were found either with univariate analysis (log rank P = .13) or after adjustment for minimization variables (hazard ratio, 0.68; 95% CI, 0.46-1.04; P = .07).

Adverse Events

One patient (1%) in the indwelling pleural catheter group vs 3 (4%) in the pleurodesis group experienced serious adverse events (Table 3). Any adverse event (n = 30) occurred in 22 patients (30%) in the indwelling pleural catheter group, whereas 13 patients (18%) in the talc group experienced 23 adverse events. Worsening breathlessness and procedure-related pain were the most common adverse events in both groups.
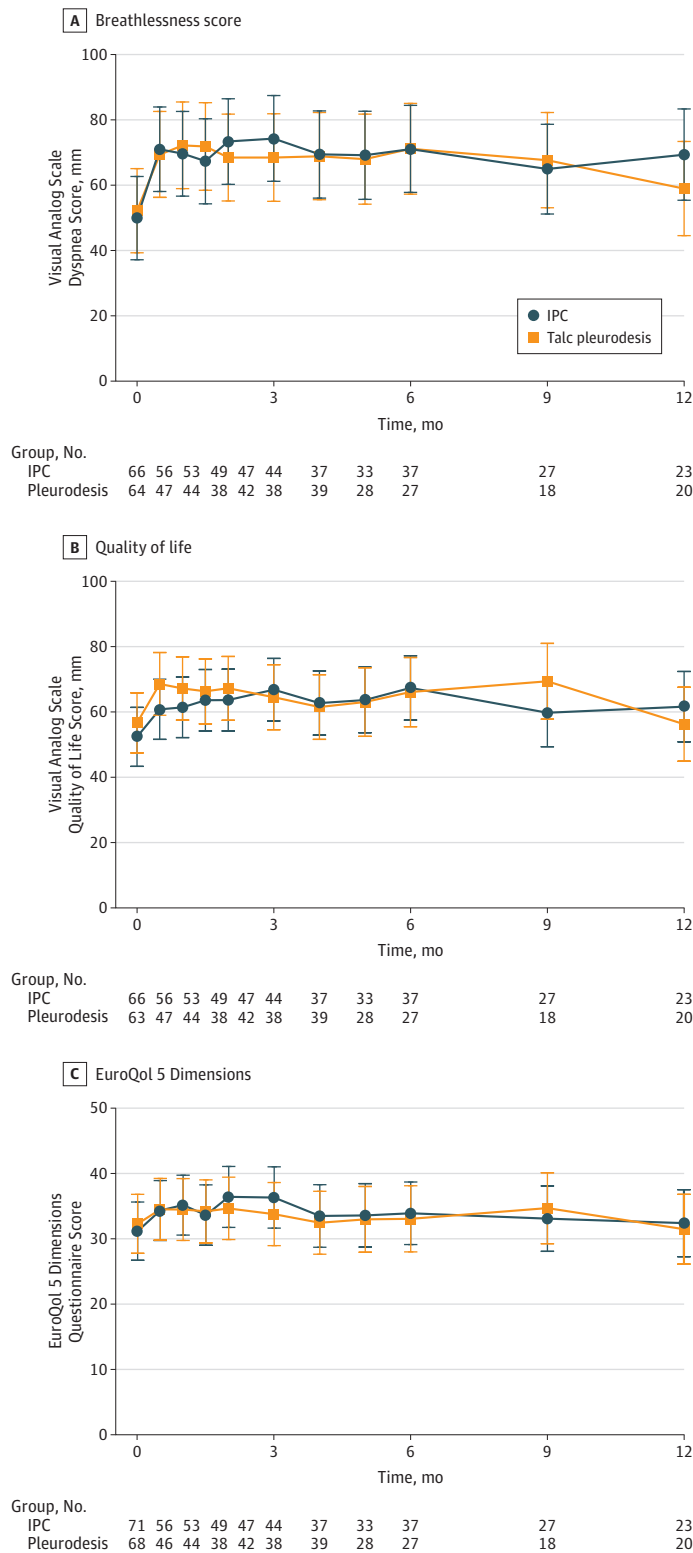
The catheter was dislodged in 4 pleurodesis patients. Three were dislodged accidentally in hospital before talc instillation. In 2 cases, the fluid did not recur while in the third case, fluid re-

curred several months later and the patient had an indwelling pleural catheter inserted. In the fourth case, the chest drain was disconnected from the drainage bottle and was reconnected; pleurodesis was performed as planned. In 1 patient with indwelling pleural catheter, the catheter was removed accidentally and the participant declined a further indwelling pleural catheter insertion. Pleural infection (n = 2), cellulitis (n = 3), symptomatic fluid loculation (n = 1), and catheter blockage (n = 3) were reported with indwelling pleural catheter management.

Post Hoc Analyses

Patients randomized to indwelling pleural catheter treatment spent significantly less time (as a percentage of their total days in trial) in hospital (median, 6.2% [IQR, 1.1%-15.0%] in the indwelling pleural catheter group vs 11.1% [IQR, 3.2%-37.0%] in the pleurodesis group; P = .01; HL estimate, 3.11%; 95% CI, 0.38%-7.95%).

Figure 3. Comparison of Patient-Reported Outcomes Between Those Randomized to Receive an Indwelling Pleural Catheter (IPC) and Those Randomized to Receive Talc Pleurodesis

A Breathlessness score

Group, No.

IPC	66	56	53	49	47	44	37	33	37	27	23
Pleurodesis	64	47	44	38	42	38	39	28	27	18	20

B Quality of life

Group, No.

IPC	66	56	53	49	47	44	37	33	37	27	23
Pleurodesis	63	47	44	38	42	38	39	28	27	18	20

C EuroQol 5 Dimensions

Group, No.

IPC	71	56	53	49	47	44	37	33	37	27	23
Pleurodesis	68	46	44	38	42	38	39	28	27	18	20

Points are estimated means from linear mixed models with error bars representing 95% CIs. Time 0 denotes the time of treatment intervention; sample size differs owing to missing data. A, Breathlessness score was measured with a visual analog scale, with a 100-mm line anchored with "no breathlessness" at 100 mm and "worst imaginable breathlessness" at 0 mm. B, Quality-of-life score was measured with a visual analog scale, with a 100-mm line anchored with "best quality of life" at 100 mm and "worst quality of life" at 0 mm. C, The EuroQol 5 Dimensions quality-of-life score consisted of 5 domains: mobility, self-care, usual activities, discomfort/pain, and anxiety/depression. Each domain was graded by the patient from 0 (worst imaginable) to 10 (best imaginable) and the total score out of a maximum 50 points was presented.

Subgroup post-hoc analyses confirmed the benefits for patients with malignant pleural effusion (n = 106) with metastatic cancers, with a median time spent in hospital of 10.0 days (IQR, 4-16) vs talc pleurodesis (median, 14.0 days [IQR, 7-22]; P = .03; HL estimate, 3.44 days; 95% CI, 0.55-7.14). The reduction in effusion-related hospitalization days from indwelling

Table 3. Summary of Serious Adverse Events and Adverse Events

Type of Adverse Event	Indwelling Pleural Catheter (n = 73)	Talc Pleurodesis (n = 71)
Serious adverse events		
Patients affected, No. (%)	1 (1)[a]	3 (4)[b]
No. of adverse events		
Pleural infection	2	1
Cellulitis	4	0
Symptomatic loculation	1	1
Catheter blockage	3	0
Pneumothorax	1	1
Pain related to procedure	6	4
Worsening breathlessness	4	6
Tube dislodgement	1	4
Others	7	3
Total adverse events, No.	29	20
Total serious adverse events, No.	1	3
Total adverse and serious adverse events, No.	**30**	**23**
Patients affected by any adverse event, No. (%)	22 (30)	13 (18)

[a] One patient experienced a pulseless electrical activity cardiac arrest following indwelling pleural catheter insertion due to underlying cardiac disease but was successfully resuscitated without sequelae.

[b] One patient died during surgery for a femoral fracture after a fall; 1 developed submassive pulmonary emboli; and 1 experienced severe chest pain requiring hospital admission.

pleural catheter treatment over pleurodesis were significant for patients with metastatic carcinoma (median, 2 days [IQR, 1-3] vs 4 days [IQR, 3-6], respectively; $P < .001$; HL estimate, 2.1 days; 95% CI, 1.48-2.71) and patients with mesothelioma (median, 1 day [IQR, 1-3] vs 3 days [IQR, 2-4]; $P = .003$; HL estimate, 1.68 days; 95% CI, 0.90-2.42).

For the initial admission, the median time in hospital for the indwelling pleural catheter and pleurodesis groups were 2 days (IQR, 1-4) vs 3 days (IQR, 3-6), respectively ($P < .001$; HL estimate, 1.85 days; 95% CI, 1.30-2.41). The median number of hospital days for subsequent hospital admissions was 4 (IQR, 0-12) for the indwelling pleural catheter group and 6 (IQR, 0-16) for the pleurodesis group; the difference was not significant ($P = .34$; HL estimate, 0.61 days; 95% CI, −0.68 to 3.57).

Missing data were not present in any of the hospital admission days outcomes and overall there were 19% missing data in QoL and breathlessness scores. For these, a subsequent sensitivity analysis was carried out using multiple imputation, the results of which were consistent with those described here (eTable in Supplement 2).

Discussion

In this trial of patients with malignant pleural effusion, treatment with an indwelling pleural catheter vs talc pleurodesis resulted in fewer hospitalization days from treatment procedure to death (or 12-month follow-up), but the magnitude of

the difference was of uncertain clinical importance. The data also showed that patients treated with indwelling pleural catheter over talc pleurodesis experienced fewer hospital days related to pleural effusion management and required fewer further invasive pleural drainages. Both indwelling pleural catheter and pleurodesis provided significant improvements in breathlessness and QoL; however, there were no significant differences between the 2 groups. These findings may inform patients and clinicians in deciding management.

Indwelling pleural catheter and pleurodesis are 2 strategies with advantages and disadvantages[22]; existing literature suggests equipoise.[8] To date, 3 RCTs[9,10,23] have compared indwelling pleural catheter with talc pleurodesis (n = 106 and n = 57) or doxycycline pleurodesis (n = 144). Both indwelling pleural catheter and pleurodesis provided comparable symptomatic benefits in these studies; neither was found superior. This trial confirmed these findings and provided new data showing an advantage of indwelling pleural catheter in reducing hospitalization. This study, to our knowledge, was the first to measure total days spent in hospital in patients' remaining lifespan as a principal outcome in malignant pleural effusion management. Malignant pleural effusions herald limited prognosis. The management goals are to relieve symptoms with minimal intervention and maximize time outside hospital. Post-hoc analysis showed that the use of indwelling pleural catheter significantly reduced the amount of time in trial patients spent in hospital (median, 6.2% vs 11.1% of their days in trial) over conventional pleurodesis.

Indwelling pleural catheter provided several advantages over talc pleurodesis that would have contributed to the reduction in the total hospitalization days before death. First, patients randomized to indwelling pleural catheter treatment had shorter initial hospital admissions because indwelling pleural catheters were placed as day-case or overnight procedures whereas pleurodesis required chest tube insertion, complete evacuation of fluid, talc instillation, and hospitalization until fluid drainage ceased. Second, talc pleurodesis failed and necessitated further drainage interventions in 23% of patients in the trial, most of whom required admissions for further interventions. This failure rate is in keeping with other trials.[6,24] Conversely, only 4% of indwelling pleural catheter–treated patients required further pleural drainages. The lower reintervention rate with indwelling pleural catheter is an important consideration and benefit for patients with advanced cancer.

The data also showed that indwelling pleural catheter–specific complications (eg, empyema) were relatively uncommon, consistent with other longitudinal studies,[25-27] and did not increase the median hospitalization days. Both QoL and breathlessness significantly improved from baseline in the indwelling pleural catheter and pleurodesis groups; however, there was no difference between the groups, a finding consistent with another previous RCT.[9]

The shortening of total hospitalization time by a median of 2 days is of uncertain clinical importance because there are no established minimal clinically important differences for this end point. This difference may be important to the hospital care system because it frees up substantial hospital beds

and resources, but its relevance to clinical decision making for individual patients may depend on patient preference and circumstances.

Further studies are under way to optimize the benefits of indwelling pleural catheter use. The AMPLE-2 trial is an RCT comparing aggressive (daily) indwelling pleural catheter drainages with symptom-guided "as-required" approach for dyspnea relief and likelihood of spontaneous pleurodesis[28] (trial registration: ACTRN12615000963527). Whether talc instillation via an indwelling pleural catheter can improve pleurodesis rate is the subject of the recently completed IPC-PLUS trial[29] (trial registration: ISRCTN73255764). Indwelling pleural catheter coated with a sclerosant (silver nitrate) has shown promise in animal studies[30] and in a pilot clinical study.[31]

Talc can be administered as slurry via a chest tube or as dry powder via thoracoscopic poudrage. Previous RCTs showed that talc slurry and poudrage have similar failure rates[6,7]; whether the different delivery methods affect lifetime all-cause hospitalization has not yet been studied. Australia has one of the world's highest incidences of mesothelioma.[32] This study therefore included more patients with mesothelioma than would otherwise be expected in many countries. The study randomization did stratify patients by mesothelioma (vs other cancers) and subgroup analyses showed benefits in reducing hospitalization days.

Limitations

This study has several limitations. First, no health economic analyses were conducted. This decision was taken as the costs of hospital days, indwelling pleural catheter equipment and drainage kits, and pleurodesis vary vastly worldwide,[33,34] including at the participating centers of this study. The investigators therefore made a decision at the start of the study not to proceed with cost analyses. However, based on the rough costs provided by the participating centers, there is a reasonable likelihood that savings from the reduction in the small number of hospitalization days found in this study will not meet the usual standards of cost-effectiveness. Clinicians need

to translate the reduction of hospital days into local cost currencies to establish the health care savings in individual health systems.

Second, variations are common on talc pleurodesis protocols and no universally accepted standard exists. In this pragmatic study, treating clinicians were allowed to perform talc pleurodesis following their center's routine practice (including drain size). A recent study suggested that pleurodesis via a 24F chest drain can improve the failure rate over 12F drains (24% vs 30%, respectively).[7] However, the margin of improvement was relatively small and unlikely to affect total hospitalization days.

Third, the rate ratios for (serious) adverse events have large confidence intervals because of the small numbers of adverse events and should be interpreted carefully. There were more nonserious adverse events in the indwelling pleural catheter group compared with the pleurodesis group. Many of these complications (eg, blocked catheters or cellulitis) needed interventions, although not necessarily hospitalizations; nonetheless, they may reduce the advantage of reducing hospital days indwelling pleural catheter has over talc pleurodesis.

Fourth, although indwelling pleural catheter provided an advantage in reduction of hospitalization days, the magnitude of difference was below the 5 days used for power calculation. Both this and a prior study[9] found that indwelling pleural catheter and talc pleurodesis provided significant QoL improvement but neither was significantly better than the other. These factors should all be incorporated in the clinical decision-making process for the individual patient.

Conclusions

Among patients with malignant pleural effusion, treatment with an indwelling pleural catheter vs talc pleurodesis resulted in fewer hospitalization days from treatment to death, but the magnitude of the difference is of uncertain clinical importance. These findings may help inform patient choice of management for malignant pleural effusion.

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