Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial

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Summary

Background Indwelling pleural catheters are an established management option for malignant pleural effusion and have advantages over talc slurry pleurodesis. The optimal regimen of drainage after indwelling pleural catheter insertion is debated and ranges from aggressive (daily) drainage to drainage only when symptomatic.

Methods AMPLE-2 was an open-label randomised trial involving 11 centres in Australia, New Zealand, Hong Kong, and Malaysia. Patients with symptomatic malignant pleural effusions were randomly assigned (1:1) to the aggressive (daily) or symptom-guided drainage groups for 60 days and minimised by cancer type (mesothelioma *vs* others), performance status (Eastern Cooperative Oncology Group [ECOG] score 0–1 *vs* ≥2), presence of trapped lung, and prior pleurodesis. Patients were followed up for 6 months. The primary outcome was mean daily breathlessness score, measured by use of a 100 mm visual analogue scale during the first 60 days. Secondary outcomes included rates of spontaneous pleurodesis and self-reported quality-of-life measures. Results were analysed by an intention-to-treat approach. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12615000963527.

Findings Between July 20, 2015, and Jan 26, 2017, 87 patients were recruited and randomly assigned to the aggressive (n=43) or symptom-guided (n=44) drainage groups. The mean daily breathlessness scores did not differ significantly between the aggressive and symptom-guided drainage groups (geometric means 13·1 mm [95% CI 9·8–17·4] *vs* 17·3 mm [13·0–22·0]; ratio of geometric means 1·32 [95% CI 0·88–1·97]; p=0·18). More patients in the aggressive group developed spontaneous pleurodesis than in the symptom-guided group in the first 60 days (16 [37·2%] of 43 *vs* five [11·4%] of 44, p=0·0049) and at 6 months (19 [44·2%] *vs* seven [15·9%], p=0·004; hazard ratio 3·287 [95% CI 1·396–7·740]; p=0·0065). Patient-reported quality-of-life measures, assessed with EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L), were better in the aggressive group than in the symptom-guided group (estimated means 0·713 [95% CI 0·647–0·779] *vs* 0·601 [0·536–0·667]). The estimated difference in means was 0·112 (95% CI 0·0198–0·204; p=0·0174). Pain scores, total days spent in hospital, and mortality did not differ significantly between groups. Serious adverse events occurred in 11 (25·6%) of 43 patients in the aggressive drainage group and in 12 (27·3%) of 44 patients in the symptom-guided drainage group, including 11 episodes of pleural infection in nine patients (five in the aggressive group and six in the symptom-guided drainage group).

Interpretation We found no differences between the aggressive (daily) and the symptom-guided drainage regimens for indwelling pleural catheters in providing breathlessness control. These data indicate that daily indwelling pleural catheter drainage is more effective in promoting spontaneous pleurodesis and might improve quality of life.

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Introduction

Malignant pleural effusion can complicate most cancers.[1] The associated breathlessness is often distressing, debilitating, and significantly impairs quality of life.[2] Malignant pleural effusion accounts for more than 125 000 hospital admissions per year in the USA alone.[3]

Indwelling pleural catheter drainage is a new therapeutic approach for management of malignant pleural effusion, and its advantages have been confirmed in randomised trials.[4,5] Treatment with an indwelling pleural catheter significantly reduces days spent in hospital and the need for further invasive pleural procedures in patients' remaining life,[4] compared with conventional talc slurry pleurodesis, while offering the same level of improvement in symptoms and quality of life.[4,5] Indwelling pleural catheters are increasingly being adopted worldwide as the first-line management option for malignant pleural effusion.

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Research in context

Evidence before the study

Malignant pleural effusions often require pleural intervention for symptom control. Results of two multicentre trials have confirmed that an indwelling pleural catheter provides similar benefits to conventional talc slurry pleurodesis with regard to symptom control and quality of life. The AMPLE-1 randomised trial found that an indwelling pleural catheter provided added advantages over talc pleurodesis in reducing days spent in hospital, in patients' remaining lifespan, and in minimising the need for repeat invasive pleural drainage procedures. Having established the advantages and safety of indwelling pleural catheter insertion for management of malignant pleural effusions, the next step was to optimise its effectiveness by identifying its best drainage regimen. We searched PubMed for articles published before March 1, 2018, using the terms "malignant pleural effusion" AND "indwelling pleural catheter OR IPC" AND "drainage frequency" AND "breathlessness OR dyspnoea". The only randomised controlled trial in the 11 articles found compared rates of spontaneous pleurodesis between daily drainage versus alternate-day drainage in 149 patients with malignant pleural effusions. However, many clinicians preferred drainage only when patients developed symptomatic breathlessness, as malignant pleural effusion management is mainly palliative. Aggressive (daily) versus infrequent symptom-guided drainage regimens have not been compared but have substantial implications for clinical care.

Added value of this study

The AMPLE-2 study addresses this equipoise by randomly assigning 87 patients with malignant pleural effusion to aggressive or symptom-guided drainage regimens via an indwelling pleural catheter. Both approaches provided similar breathlessness control over 60 days after randomisation. Pain scores, days spent in hospital, serious adverse events, and mortality did not differ significantly between the two groups. Aggressive drainage was associated with higher rates of pleurodesis than symptom-guided drainage and better index values on EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) quality-of-life assessment.

Implications of all the available evidence

For patients with malignant pleural effusion treated with an indwelling pleural catheter in whom early catheter removal is an important goal, daily drainage should be carried out for at least 60 days. For patients whose primary care aim is palliation, our data suggest that symptom-guided drainage offers an effective means of breathlessness control without the burden and costs of daily drainages. A recent randomised study found that talc pleurodesis can be administered via indwelling pleural catheter and enhance pleurodesis and catheter removal rate. Combining this approach with aggressive daily drainage after talc instillation to enhance the rate of successful pleurodesis should be assessed.

The logical next step is to optimise the use of this approach and hence its benefits. Few data exist to guide drainage approaches for patients with an indwelling pleural catheter. Practices vary worldwide, ranging from aggressive (daily or alternate-day) drainage, often used in centres in the USA,[6] to drainage only when symptoms develop, which is common in the rest of the world. These differences in practice could potentially influence outcomes and complication rates.

Aggressive daily drainage arguably keeps the pleural space dry and provides best symptom control every day, whereas health-care practitioners who advocate symptom-guided drainage contend that the goal of malignant pleural effusion care is palliation and that drainage of indwelling pleural catheter is only indicated when symptoms arise. The symptom-guided approach might reduce a substantial amount of burden and consumable costs compared with daily drainage, and might reduce the risk of iatrogenic introduction of pleural infection.

Conversely, frequent indwelling pleural catheter drainage might facilitate approximation of the visceral and parietal pleura and facilitate their symphysis (so-called spontaneous pleurodesis), and allow removal of the catheter. Daily drainage has been shown to promote pleurodesis more effectively than alternate-day drainage.[6] Whether a symptom-guided approach affects the rate of pleurodesis is unknown.

The Australasian Malignant PLeural Effusion-2 (AMPLE-2) study was designed to address the equipoise between aggressive (daily) versus symptom-guided approaches to indwelling pleural catheter drainage in patients with a malignant pleural effusion—specifically, their efficacy in breathlessness control, induction of pleurodesis, improvement of quality of life, reduction of days spent in hospital, and complication rates.[7]

Methods

Study design and patients

The AMPLE-2 study was a randomised, multicentre, open-label trial. Patients were enrolled from 11 centres: Sir Charles Gairdner, Fiona Stanley, Royal Perth, Saint John of God Bunbury, Sunshine Coast University, Royal Adelaide, Wesley, and St George & The Sutherland Hospitals in Australia; Middlemore Hospital in New Zealand; Queen Elizabeth Hospital, Kota Kinabalu, in Malaysia; and Queen Mary Hospital in Hong Kong. The study protocol has been published.[7] Ethics and governance approvals were obtained from the human research ethics committee at all sites, with the primary committee being the Sir Charles Gairdner and Osborne Park Health Care Group Human Research and Ethics Committee (2014–079). Written informed consent was obtained from all patients.

All patients enrolled were adults who required indwelling pleural catheter placement for management of

a malignant pleural effusion. All patients had malignant cells identified in the pleural fluid or pleural biopsy tissue; or a large exudative pleural effusion without other causes in a patient with known disseminated extrapleural malignancy. Exclusion criteria were age younger than 18 years, expected survival less than 3 months, pleural infection, chylothorax, pregnancy, lactation, uncorrectable bleeding diathesis, previous ipsilateral lobectomy or pneumonectomy, significant loculations likely to preclude effective fluid drainage, significant visual impairment, and inability to consent or comply with the study protocol.

Randomisation and masking

Randomisation was done independently by the National Health & Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Australia. Patients were randomly assigned (1:1) to aggressive (daily) or symptom-guided drainage via their indwelling pleural catheter, by use of an automated telephone-based voice-response randomisation service. Randomisation code generation was assigned sequentially as patients underwent the randomisation process. Randomisation was minimised for cancer type (mesothelioma *vs* non-mesothelioma), performance status (Eastern Cooperative Oncology Group [ECOG] score 0–1 *vs* ≥2), presence of trapped lung (*vs* its absence), and prior pleurodesis (*vs* no prior pleurodesis). Trapped lung was defined as air or fluid in the pleural space occupying 25% or more of the lateral chest wall after initial drainage. Minimisation is a dynamic method; as such, there was no sequence generation. Allocation concealment was additionally maintained by incorporating an imbalance window (set at 3) within which treatments were completely random (the order of the random allocations was maintained within the NHMRC Clinical Trials Centre secure database). Patients who withdrew from the trial were not replaced. Masking of patients or those giving the interventions was not practical or possible.

Procedures

The indwelling pleural catheter (Rocket Medical plc, Washington, UK) was inserted as per standard clinical practice. Patients were randomly assigned within 72 h of indwelling pleural catheter insertion after maximum pleural fluid evacuation to ensure the same baseline for all patients. In the aggressive drainage group, patients (or their carers or community nurses) were asked to drain the malignant pleural effusion via the indwelling pleural catheter every day for the first 60 days unless clinically contraindicated, or unless spontaneous pleurodesis had occurred. For the symptom-guided group, patients carried out drainage when they had effusion-related symptoms (usually breathlessness, cough, or chest tightness). The indwelling pleural catheter was accessed at least fortnightly to ensure it remained patent and to assess whether fluid was still being produced.

Patients were supplied with standard indwelling pleural catheter vacuum-suction bottles (600 mL) for fluid drainage, following instructions of the manufacturer. Pleurodesis was defined as less than 50 mL of fluid removed at three consecutive drainages[6] (in the aggressive drainage group) or at two attempts 2 weeks apart (in the symptom-guided group), and in the absence of substantial residual pleural fluid collections on imaging.

All patients and carers were given a standard briefing about the drainage method, aftercare, and potential complications, and had ready access to support services (eg, via direct phone line) for any concerns. They were free to receive other treatments including chemo-irradiation and palliative care as recommended by treating clinicians. Patients were followed up for a minimum of 6 months after randomisation or until death, whichever occurred first. The drainage regimen after 60 days was left to the discretion of the attending clinicians.

Patients kept a logbook of their breathlessness score recorded every day for 60 days and then weekly until the end of the study. The breathlessness score was measured by use of a validated 100 mm visual analogue scale (VAS), a 100 mm line anchored with "best breathing" at 0 mm and "worst breathing imaginable" at 100 mm. The pain level was also measured on a 100 mm VAS, which was anchored with "no pain" at 0 mm and "worst imaginable pain" at 100 mm.[8] The volume of pleural fluid removed at each drainage was also recorded.

Baseline clinical data, VAS scores for breathlessness[4,5,9] and pain, and quality-of-life measures (VAS and EuroQoL-5 Dimensions-5 Levels [EQ-5D-5L][10]) were collected before indwelling pleural catheter insertion and after randomisation (within 72 h after insertion). Patients were followed up at 2 weeks and 4 weeks, and thereafter monthly for 6 months. Details of any hospital admissions were recorded, including duration, adverse events, and clinical management.

Outcomes

The primary outcome was the mean daily breathlessness score in the first 60 days after randomisation. The VAS scores were measured by two independent assessors and the average of their readings recorded. Both assessors repeated their measurements separately if initial readings differed by more than 3 mm. If discrepancies persisted, the assessors would re-score and discuss to reach a consensus.

Secondary outcomes included rates of spontaneous pleurodesis and self-reported global quality-of-life measurements with two instruments, namely the EQ-5D-5L[11,12] and a 100 mm VAS at randomisation (after maximal fluid drainage), at pre-determined clinic follow-up visits 2 weeks and 4 weeks after randomisation, and thereafter monthly for up to 6 months. The EQ-5D-5L score consisted of five domains: mobility,

	Aggressive (daily) drainage (n=43)	Symptom-guided drainage (n=44)
Age (years)	65·1 (57·8–72·5)	68·0 (60·8–75·0)
Men	21 (49%)	20 (45%)
Women	22 (51%)	24 (55%)
Side of intervention: right	27 (63%)	31 (71%)
Type of primary malignancy		
Mesothelioma	15 (35%)	14 (32%)
Non-mesothelioma	28 (65%)	30 (68%)
Lung	17 (40%)	17 (39%)
Breast	0 (0%)	4 (9%)
Ovarian	6 (14%)	4 (9%)
Other	5 (12%)	5 (11%)
Trapped lung	14 (33%)	14 (32%)
Previous talc pleurodesis	4 (9%)	7 (16%)
ECOG performance status		
0–1	30 (70%)	30 (68%)
≥2	13 (30%)	14 (32%)
Comorbidities		
Respiratory	8 (19%)	13 (30%)
Cardiac	9 (21%)	8 (18%)
Depression or anxiety	9 (21%)	6 (14%)
Diabetes	6 (14%)	6 (14%)
Effusion size grade*		
Small (0–1)	1 (2%)	1 (2%)
Moderate (2–3)	13 (30%)	14 (32%)
Large (4–5)	29 (67%)	29 (66%)
Baseline self-reported symptom scores		
VAS breathlessness score (mm)	28·1 (20·3)	28·3 (20·7)
VAS QoL score (mm)	36·4 (22·4)	29·8 (19·9)
EQ-5D-5L index score	0·681 (0·177)	0·611 (0·231)
EQ-5D-5L score by modality median (IQR)		
Mobility	1 (1–2)	2 (1–3)
Self-care	1 (1–2)	1 (1–2)
Usual activities	2 (2–3)	2 (1–3)
Pain or discomfort	2 (2–3)	2 (2–3)
Depression or anxiety	1 (1–2)	2 (1–2)
Chemotherapy in preceding 30 days	9 (21%)	11 (25%)

Data are median (IQR), n (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group. VAS=visual analogue scale. QoL=quality of life. EQ-5D-5L=EuroQoL-5 Dimensions-5 levels. *Baseline effusion size was graded on chest radiograph by use of a validated grading system whereby grade 0 referred to no radiographic evidence of pleural fluid; grade 1 to blunting of the costophrenic angle; grade 2 to fluid occupying less than 25% of the hemithorax, grade 3 to fluid occupying 25–50%, grade 4 to fluid occupying 51–75%, and grade 5 to fluid occupying more than 75%.[16] This scale has previously been used to predict pleurodesis and indwelling pleural catheter use in patients with a malignant pleural effusion.[17]

Table 1: **Summary statistics of baseline measures provided by treatment group**

self-care, usual activities, discomfort or pain, and anxiety or depression. Each domain was graded by the patient from 1 (no problems) to 5 (worst). The quality-of-life score was also measured with a 100 mm line anchored with "best quality of life" at 0 mm and "worst quality of life" at 100 mm. Another secondary outcome was the total number of episodes and duration of hospital stay for any cause (excluding elective admissions for chemotherapy). Hospital admissions were subdivided into pleural-related (or not) hospital days, as defined previously,[4] from randomisation to death or end of 6-month follow-up, whichever occurred first. Other secondary outcomes were the frequency of adverse events and serious adverse events, which were assessed by an independent reviewer for relatedness to the trial intervention, and survival.

Statistical analysis

Data were analysed on an intention-to-treat basis and supporting analyses were done adjusting for minimisation variables measured at randomisation of mesothelioma, ECOG score, the presence of a trapped lung, and prior pleurodesis, in addition to the random effect of study centre, where appropriate. All data were analysed with the R environment for statistical computing[13] and SAS/STAT software, version 9.4.

The study was designed to enrol at least 86 patients to detect a mean difference in VAS score of 14 mm between the treatment groups (5% significance, 90% power) assuming a common between-group SD of 18·9 mm (based on a previous randomised controlled trial of treatment with an indwelling pleural catheter[5]) and a 10% lost-to-follow-up rate. The minimal clinically important difference for the VAS score in this setting was 19 mm (95% CI 14–24) as per the study by Mishra and colleagues.[9] The lower end of the 95% CI of 14 mm was used for this power calculation.

The difference in breathlessness scores and pain scores between the two groups was analysed with a two-sample *t* test on the log-transformed average scores in the first 60 days of the trial. Results are back-transformed and presented as geometric means and 95% CIs and compared through a ratio of the geometric means. A two-sample *t* test was used to compare the difference in rates of logbook completion between the two groups.

Time to spontaneous pleurodesis was analysed with the Fine and Gray competing risks survival model, with competing risk being death, and described with the cumulative incidence curve. Time to death was analysed with Kaplan-Meier survival curves and Cox proportional hazards models. For all time-to-event analyses, hazard ratios (HRs) and 95% CIs comparing the two groups are provided. Differences in proportions of survival and spontaneous pleurodesis between the groups were compared with χ^2 tests for independence or Fisher's exact tests. All hospital admissions data were analysed with Mann-Whitney tests to compare the two groups with supporting analyses by use of negative binomial regression models. The EQ-5D-5L[11,12] scores were converted into a single index value that generates a measure of utility ranging from –0·111 to 1·000 (where

1·000 indicates full health) via an online tool.[14] A crosswalk value set[15] was used to obtain the index value, as no EQ-5D-5L value set was available specifically for the countries included in this study. Linear mixed models were used to compare EQ-5D-5L index values and log-transformed VAS quality-of-life scores between the two groups. Fixed effects of treatment, time, and the treatment by time interaction and random patient and study centre effects were included in the model along with effects of minimisation variables and, in supporting analyses, the effect of baseline index values. Differences in least squares means (95% CI) or ratios of geometric means (95% CI) are provided. In instances where the logbook entries were incomplete, supporting sensitivity analyses were done with multiple imputation by use of chain equations of 40 imputed datasets.

This trial is registered with the Australian New Zealand Clinical Trial Registry, ACTRN12615000963527.

Role of the funding source

The funders of the study had no role in study design and conduct, data collection, data management, data analysis, or data interpretation, in preparation, review, or approval of the manuscript, or in the decision to submit the manuscript for publication. SM and YCGL have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses and had full responsibility for the decision to submit for publication.

Results

Between July 20, 2015, and Jan 26, 2017, 87 patients (median age 66·8 years [IQR 59·1–74·3]; 41 men and 46 women) were recruited and randomly assigned to the aggressive (n=43) or symptom-guided (n=44) drainage groups. The groups were well matched for age, sex, proportions of primary malignancies and trapped lung, effusion size, comorbidities, baseline symptom scores, and ECOG status (table 1). The most common underlying malignancies were lung cancer (n=34), mesothelioma (n=29), and ovarian carcinoma (n=10).

Those randomly assigned to the aggressive group underwent 1420 drainages (median 39 [IQR 13–57] per participant) for up to 60 days (the intervention period), until time of pleurodesis or death (whichever occurred earliest), of a possible 1518 drainages, confirming good compliance. Patients in the symptom-guided group underwent 535 drainages (median 11 [IQR 7–18] per participant) in the same period. At the end of the 6-month follow-up period, the total number of drainages done was 1999 in the aggressive drainage group and 1035 in the symptom-guided group.

Data were analysed on an intention-to-treat basis (figure 1). Five patients did not return their logbook and therefore had no breathlessness score data; they were excluded from the primary endpoint analysis. Compliance rates of reporting daily breathlessness scores did not differ significantly between the two groups (81·8% in the aggressive drainage group *vs* 79·7% in the symptom-guided group, p=0·74).

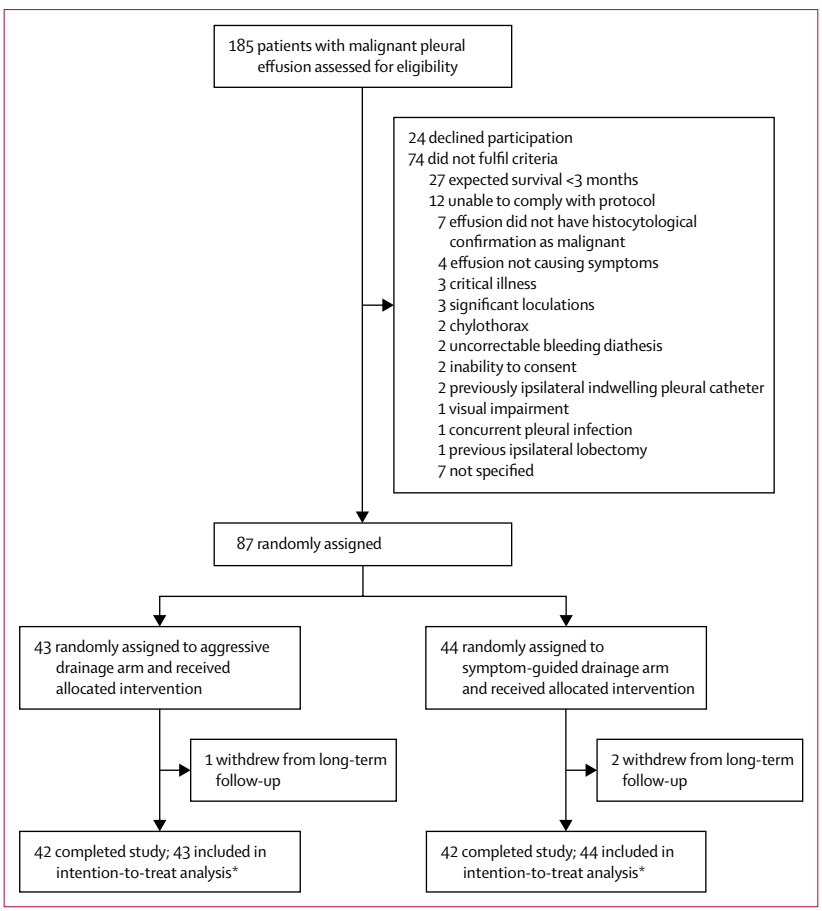

Figure 1: **Trial profile**
*Five patients (two in the aggressive drainage group and three in the symptom-guided drainage group) did not return any logbook data for primary endpoint analysis.

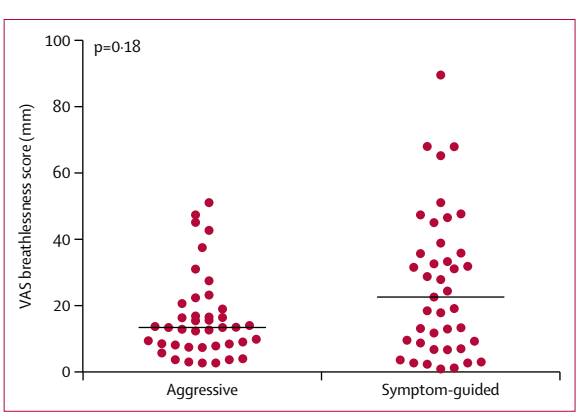

Figure 2: **Average VAS breathlessness scores of each patient over the first 60 days, by treatment group**
The minimal clinically important difference of this instrument is 19 mm for patients with malignant pleural effusion. Horizontal lines indicate the median values. VAS=visual analogue scale.

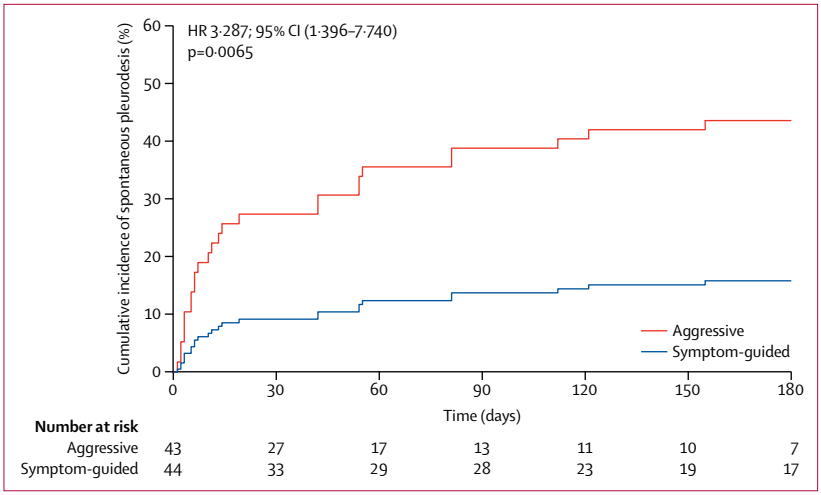

Figure 3: **Cumulative incidence curve of pleurodesis success rate based on 6 months' data estimated from Fine and Gray competing risks model**
Three patients withdrew from the study during the 6-month follow-up: one from the aggressive drainage group at 173 days and two from the symptom-guided drainage group at 52 and 97 days. HR=hazard ratio.

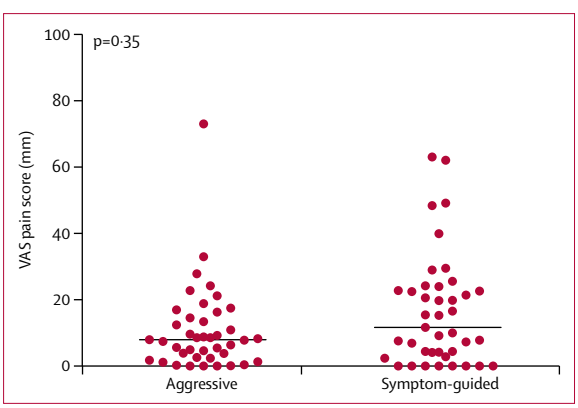

Figure 4: **Average VAS pain scores of each patient over the first 60 days**
Horizontal lines indicate median values. VAS=visual analogue scale.

The primary outcome did not differ significantly between the two groups (geometric mean 13·1 mm [95% CI 9·8–17·4] with aggressive drainage *vs* 17·3 mm [13·0–22·0] with symptom-guided drainage; ratio of geometric means 1·32 [95% CI 0·88–1·97]; p=0·18; figure 2). This outcome was further supported in analyses adjusting for minimisation variables and including random centre effects (geometric mean 16·3 mm [95% CI 11·3–23·7] with aggressive drainage *vs* 21·0 mm [14·8–29·7] with symptom-guided drainage, p=0·21; ratio of geometric means 1·28 [95% CI 0·86–1·91]) and was consistent when multiple imputation was done to account for missing logbook entries.

See Online for appendix

The frequency of spontaneous pleurodesis was significantly higher in the aggressive drainage group (16 [37·2%] of 43 patients) than in the symptom-guided group in the first 60 days (five [11·4%] of 44; p=0·0049), and after 6 months (19 [44·2%] *vs* seven [15·9%], p=0·004). The competing risk survival model indicated higher likelihood of development of spontaneous pleurodesis in the aggressive drainage group than in the symptom-guided group (HR 3·287, 95% CI 1·396–7·740; p=0·0065; figure 3). These results were consistent after adjusting for minimisation variables (HR 3·429 [95% CI 1·413–8·320]; p=0·0064).

We compared patients with non-trapped (n=59) and trapped lungs (n=28) in a post-hoc analysis. Spontaneous pleurodesis was more common in those with non-trapped lungs than in those with trapped lungs (17 [28·8%] *vs* four [14·3%]) at 60 days but not at 6 months (18 [30·5%] *vs* eight [28·6%]). In the aggressive drainage group, spontaneous pleurodesis developed in 12 (41·4%) patients with non-trapped lungs compared with four (28·6%) with trapped lungs at 60 days and in 12 (41·4%) compared with seven (50·0%) at 6 months. In the symptom-guided group, spontaneous pleurodesis developed in five (16·7%) patients with non-trapped lungs, compared with none in those with trapped lungs at 60 days and in six (20·0%) compared with one (7·1%) at 6 months. The Kaplan-Meier estimated median time to pleurodesis was 121 days in the aggressive drainage group, including in those with trapped and non-trapped lungs. The success rate was too low in the symptom-guided group to provide a reliable Kaplan-Meier estimate of the median time to pleurodesis.

The mean VAS pain score during the first 60 days of the trial was 10·74 mm (SD 12·80) in the aggressive drainage group and 16·31 mm (16·58) in the symptom-guided group (figure 4), with no significant difference between the groups (ratio of geometric means 1·28 [95% CI 0·76–2·18], p=0·35).

In a linear mixed model of response to EQ-5D-5L, no interaction between time and treatment was detected, and patient-reported quality-of-life measures over the study period and follow-up visits were better in the aggressive drainage group than in the symptom-guided drainage group (estimated means 0·713 [95% CI 0·647–0·779] *vs* 0·601 [0·536–0·667]). The estimated difference in means was 0·112 (95% CI 0·0198–0·204; p=0·0174). This finding was consistent after adjusting for minimisation variables and baseline EQ-5D-5L index values (estimated difference in means 0·097 [95% CI 0·004–0·191], p=0·0408). No between-group differences were found in the VAS quality-of-life scores during the study visits (ratio of geometric means 1·220 [95% CI 0·871–1·709], p=0·25). For all visit times for both groups there was concordance in the measures of EQ-5D-5L and the VAS quality-of-life score with significant correlations at most visit times and moderate to high correlations throughout (appendix).

The median number of hospital admissions for the entire cohort was one [IQR 0–2] for the first 60 days and two [1–3] at 6 months. Overall, patients spent 1 day [IQR 0–8] in total in hospital by 60 days and 5 days [0–15] by 6 months. The number of hospital admissions or duration spent in hospital (either in total number of days

or when only the effusion-related admissions were included (as defined in our previous trial[4]) did not differ significantly between the two groups (table 2). These results were consistent after adjusting for days enrolled in the trial and other minimisation variables.

Patients with better ECOG performance status (score 0–1) spent fewer effusion-related days in hospital at 60 days (1 [IQR 0–2] *vs* 2 [0–6] days, p=0·0392) and by 6 months (1 [IQR 0–4] *vs* 2 [0–6] days, p=0·0339) than did those with ECOG performance status scores of 2 or greater. Trapped lung at baseline was associated with fewer episodes of hospital admissions (one [IQR 0–2] *vs* two [1–3] without trapped lung, p=0·0406), as well as total (2·5 [IQR 0·0–6·0] *vs* 6·0 [1·0–19·0], p=0·0013) and effusion-related days spent in hospital (1 [IQR 0–3] *vs* 1 [0–6] day, p=0·0158) at 6 months.

Time to death at 6 months did not differ significantly between the aggressive drainage and symptom-guided drainage groups (HR 0·951 [95% CI 0·499–1·812]; p=0·88; figure 5). In the first 60 days, ten (23·3%) patients in the aggressive drainage group and nine (20·5%) in the symptom-guided drainage group died (estimated difference in proportions 0·028, 95% CI –0·146 to 0·202, p=0·75). By 6 months, 18 (41·9%) patients in the aggressive drainage group and 19 (43·2%) in the symptom-guided drainage group had died (estimated difference in proportions –0·013, 95% CI –0·221 to 0·195, p=0·90).

Patients with better performance status by ECOG score also had longer survival (HR 0·399 [95% CI 0·203–0·785] for death [for better to poorer ECOG status], p=0·0078) at 6 months.

The total numbers and proportions of patients with one or more adverse event or serious adverse event are presented in table 3. Of the 32 serious adverse events and 46 adverse events recorded, 11 (four serious adverse events and seven adverse events) were deemed definitely not related to the trial intervention by an independent assessor. 11 patients in the aggressive drainage group and 12 in the symptom-guided drainage group had serious adverse events. Adverse events occurred in 13 patients in the aggressive drainage group and in 22 in the symptom-guided drainage group. In the symptom-guided group, the most common adverse event was pain at the indwelling pleural catheter site requiring narcotics (n=12). Worsening dyspnoea due to ipsilateral pleural effusion despite drainage occurred in six patients, which usually responded well to increasing drainage frequency.

11 episodes of pleural infection developed (five in the aggressive drainage group and six in the symptom-guided drainage group) in nine patients over 6 months. Four patients had their indwelling pleural catheter removed at the time of infection and three others developed pleurodesis after infection. There were no deaths related to indwelling pleural catheter infection.

	Aggressive (daily) drainage (n=43)	Symptom-guided drainage (n=44)	p value
Episodes of hospital admission			
First 60 days	1 (0–2)	1 (0–2)	0·74
At 6 months	2 (1–4)	2 (1–3)	0·80
Total days spent in hospital			
First 60 days	1 (0–7)	1·5 (0·0–8·0)	0·84
At 6 months	5 (0–15)	4·0 (1·0–15·5)	0·52
Days spent in hospital that were effusion-related			
First 60 days	1 (0–4)	1 (0–3)	0·74
At 6 months	1 (0–5)	1 (0–5)	0·70

Data are median (IQR), unless otherwise stated.

Table 2: **Data of hospital admissions in episodes and duration by treatment groups**

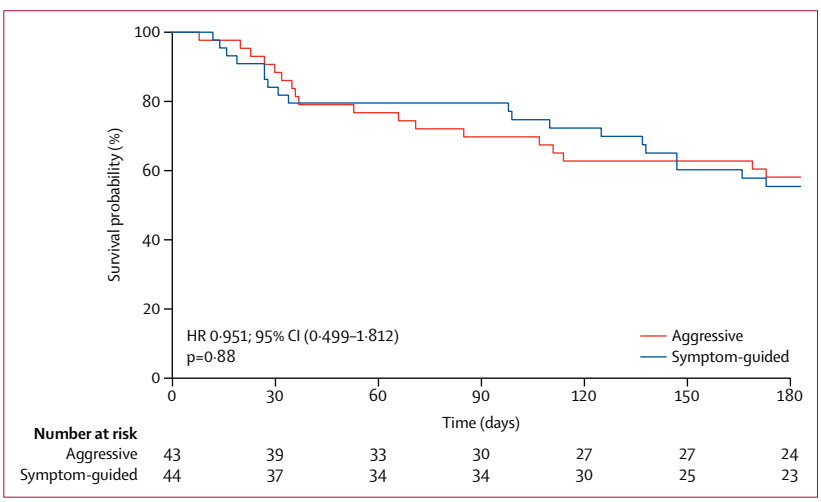

Figure 5: **Kaplan-Meier curve of survival at 6 months**
HR=hazard ratio.

Discussion

This multicentre randomised controlled trial showed no differences between the aggressive (daily) and the symptom-guided drainage approaches in providing breathlessness control over the first 60 days after indwelling pleural catheter insertion. There were no significant between-group differences in pain, days spent in hospital, or survival. Aggressive drainage was associated with a higher rate of pleurodesis and better EQ-5D-5L index values than symptom-guided drainage. Serious adverse events were uncommon in either group.

Malignant pleural effusions are common and affect about a third of patients with lung and breast cancers and the majority of patients with mesothelioma. Malignant pleural effusion often heralds incurable cancers and limited prognosis.[18] Control of the associated breathlessness frequently requires invasive pleural procedures. Use of an indwelling pleural catheter presents an alternative to conventional talc pleurodesis, and has been shown to reduce days spent in hospital,[5,19] and the need for repeat

	Aggressive (daily) drainage (n=43)	Symptom-guided drainage (n=44)
Total serious adverse events	16	16
Total adverse events	14	32
Total adverse events and serious adverse events	30	48
Number of patients with a serious adverse event	11	12
Number of patients with an adverse event	13	22
Events assessed to be "definitely", "probably", "possibly", or "unlikely to be" related to trial intervention by an independent assessor		
Serious adverse events		
Pleural infection	5	6
Symptomatic loculation	3	5
Air leak or pneumothorax	2	1
Recurrence needing re-intervention after removal of indwelling pleural catheter	1	1
Indwelling pleural catheter site cellulitis requiring hospital admission	2	0
Indwelling pleural catheter blockage requiring hospital admission	0	1
Worsening dyspnoea (effusion-related) requiring hospital admission	0	1
Adverse events		
Indwelling pleural catheter blockage	1	3
Indwelling pleural catheter site cellulitis	1	2
Pain requiring narcotics		
Indwelling pleural catheter site	7	12
Related to suction bottle	1	1
Indwelling pleural catheter leakage	0	1
Indwelling pleural catheter valve dislodged	0	1
Worsening dyspnoea		
Effusion-related	1	6
Recurrence needing re-intervention	0	1
Not effusion-related	0	1

Six events in the aggressive drainage group and five in the symptom-guided drainage group were assessed to be definitely not related to the trial intervention.

Table 3: **Adverse and serious adverse events by treatment groups**

pleural interventions in the patient's remaining lifespan.[4,5] The use of indwelling pleural catheters is growing rapidly, especially in developed countries, and is often advocated as the first-line definitive therapy for malignant pleural effusion.[20] Ambulatory indwelling pleural catheter drainages do require resources (time of carers and/or community nurses, and consumables) and can theoretically introduce infections.[21] Two approaches to indwelling pleural catheter management—aggressive and symptom-guided drainage—have evolved and are at equipoise.

Our study found no significant differences in breathlessness control, the principal goal of malignant pleural effusion palliation, whether the patients did drainages daily or as guided by symptoms. These data are reassuring and imply that, if assigned to do so, patients were able to recognise early, or anticipate, their symptoms and perform drainages before any discomfort reached a level of impact.

However, aggressive daily fluid removal did promote more effective pleurodesis. Keeping the pleural cavity fluid-free theoretically allows better approximation of the visceral and parietal pleura and thus adhesion formation and pleural symphysis. Conversely, permitting asymptomatic accumulation of the pleural fluid in between symptom-guided drainages might have physically impaired pleural symphysis. A previous randomised controlled trial also found that spontaneous pleurodesis occurred more commonly with daily rather than alternate-day drainages.[6]

Spontaneous pleurodesis in the aggressive drainage group mostly developed within the first 60 days, consistent with the timeframe from published data.[6,17] In our protocol, the drainage schedules after 60 days were left to the choice of the attending clinicians and patients. Without the suggestion of slowing down drainage, many patients might have adopted a less aggressive approach. Whether prolonging daily drainage beyond 60 days will facilitate late pleurodesis requires further research.

Our study is one of the very few randomised controlled trials that included patients with a trapped lung, which accounted for a third of the cohort, consistent with commonly quoted data. Those with trapped lung had (expectedly) a lower rate of pleurodesis than did those with an expandable lung, though aggressive drainage was still associated with a higher pleurodesis rate even in the trapped lung group. The exact mechanism will need exploration, although it is possible that in some cases the trapped lung can slowly expand with time, concurrent therapy, or a combination of both, and allow pleural symphysis. Alternatively, the trapped space might be small and when sufficient adhesions or loculations develop over time, no further fluid drainage is necessary. Nonetheless, future studies should incorporate patients with trapped lung to guide best care.

Reassuringly, aggressive drainage was not associated with more pain or infection than that observed with symptom-guided drainage. Pleural infection related to an indwelling pleural catheter affected about 5% of patients in our previous international study.[22] Daily access of the catheter might increase the risks of introducing microbes; however, pleural drainage is the key to empyema management, and aggressive drainage might ensure prompt removal of any microbes that have entered the pleural cavity. There were also no major differences in the frequency of other serious adverse events or survival between the two groups. More adverse events were observed in the symptom-guided drainage group, especially dyspnoea attributed to pleural effusion, most of which responded to increased frequency of drainage.

Patients in the aggressive drainage group reported better EQ-5D-5L index values, despite no clear benefits in their reported breathlessness or pain scores. There is no minimal clinically important difference specifically

assigned for patients with malignant pleural effusion for EQ-5D-5L or VAS quality-of-life scores. In our study, the between-group difference of the EQ-5D-5L index value was 0·112, which is above the minimal clinically important difference of 0·09 defined by Pickard and colleagues[23] in patients with advanced cancers. Daily removal of the fluid might have provided benefits in symptoms not captured with our breathlessness and pain measurements. The higher pleurodesis rate, with resultant freedom from fluid (and symptom) recurrence and of the catheter, might have contributed to the better reported quality of life. Additionally, it has been suggested that indwelling pleural catheter drainage gives patients an important sense of control when they are feeling helpless with their advancing cancer. Whether this effect can explain the scores observed in our study remains to be tested. The two quality-of-life instruments both showed improvements and good correlations of the values between the EQ-5D-5L and VAS quality-of-life scores at each time point. The between-group differences were significant with EQ-5D-5L but not with VAS quality-of-life scores. This difference might be related to the sensitivity of the instruments in detecting changes in this patient population, but this is a topic for future studies.

Developing the full potential of indwelling pleural catheters in malignant pleural effusion care is a topic of active research. Combining an indwelling pleural catheter with pleurodesis, either by instillation[17] via the catheter or coating[24] of the catheter with a pleurodesing agent, appears promising. Defining the best drainage regimen will hold an even more important role if instillation of pleurodesing agents becomes routine practice. A randomised trial[17] showed that instillation of talc slurry (followed by indwelling pleural catheter drainage two to three times a week) induced a higher rate of pleurodesis than saline control. However, the success rate in the talc group was low (around 43%), similar to what was achieved with aggressive drainage (without talc) in our trial. The results of our trial and the ASAP study[6] both confirm that daily indwelling pleural catheter fluid removal enhances spontaneous pleurodesis, which is adopted now into protocols of ongoing studies (eg, EPIToME and OPTIMUM[25]) evaluating talc instillation via indwelling pleural catheter.

Our study has various limitations. First, the primary endpoint was set at 60 days as this reflects the short median survival of patients with malignant pleural effusion from lung cancers (the most common type of malignant pleural effusion globally). We did, however, also include many patients with malignant pleural effusions from mesothelioma (the subtype with longest median survival among common causes of malignant pleural effusions). Our results did not differ between patients with non-mesothelioma and those with mesothelioma. Second, the definition of spontaneous pleurodesis used in the published literature describes cessation of fluid formation, which might relate to treatment or the natural disease course, but not necessarily to symphysis of the visceral and parietal pleura (the true meaning of pleurodesis). Ultrasound assessment was available in a subset of 18 patients who had spontaneous pleurodesis in the lead centre; all but one achieved sonographic appearances of pleural symphysis. Third, the consumable and carer costs of daily drainage vary substantially around the world. However, this study has provided an approximation of the amount of drainage consumables needed for aggressive and symptom-guided drainage, which would allow clinicians to estimate local costs of each regimen. Fourth, as our study was an open label study, the use of patient-reported measures could potentially contain bias.

Data from recently published randomised controlled trials in malignant pleural effusion management support the use of an indwelling pleural catheter as first-choice definitive management in patients with malignant pleural effusion,[4,5,26,27] but the optimal drainage schedule must be identified to realise the full potential of this intervention. The AMPLE-2 trial showed that either aggressive or symptom-guided drainage regimens are adequate in providing breathlessness control. However, daily fluid removal enhances spontaneous pleurodesis and might improve quality of life without any drawbacks in relation to pain, infection rates, or survival. In patients in whom pleurodesis is an important goal (eg, those undertaking strategies involving an indwelling pleural catheter plus pleurodesing agents), aggressive drainage should be done for at least 60 days. Future studies will need to establish if more aggressive (eg, twice daily) regimens for the initial phase could further enhance success rates.[28] However, for patients whose primary care aim is palliation (eg, those with very limited life expectancy or significant trapped lung where pleurodesis is unlikely), our data show that symptom-guided drainage offers an effective means of breathlessness control without the inconvenience and costs of daily drainages. The ability to predict the likelihood of pleurodesis will help guide the choice of regimen and should be a topic of future studies.

Contributors

YCGL was the guarantor of this Article. SM and YCGL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YCGL, SM, MA, RT, NAM, DF-K, and KM were responsible for trial conception and design and for development of the study protocol. DBF, RS, BCHK, DCLL, CCDeC, MRSRA, EY, CLT, LAG, PTN, CS, and NDP were responsible for patient recruitment and data collection. KM and CAB did the statistical analyses. CAR was responsible for trial and database management. CK was responsible for independent review of hospital discharge and adverse events data. All authors were involved in writing and final approval of the manuscript.

Declaration of interests

YCGL, DF-K, and NAM have served on the advisory board of CareFusion/BD Ltd. NAM has received an unrestricted educational grant from Rocket Medical plc (UK) and from CareFusion/BD. YCGL has received an unrestricted educational grant from Rocket Medical plc (UK). All other authors declare no competing interests.

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