



THE CLINICAL QUESTION

To compare aggressive (daily) versus symptom-guided approaches to indwelling pleural catheter (IPC) drainage in patients with malignant pleural effusion.

TAKE HOME MESSAGE

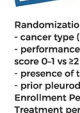
- This study showed no differences between the aggressive (daily) and the symptom-guided drainage approaches in improving breathlessness over the first 60 days after IPC insertion.
- There were no significant between-group differences in pain, days spent in hospital, or survival.
- Serious adverse events were uncommon in either group.
- Aggressive drainage was associated with a higher rate of pleurodesis and better EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) quality-of-life assessment than symptom-guided drainage (mobility, self-care, usual activities, discomfort or pain, and anxiety or depression).
- The kind of drainage regimen can thus be chosen based on the primary aim of IPC insertion (pleurodesis vs. palliation)

BACKGROUND

IPCs are now increasingly being used as first-line therapy to manage malignant pleural effusions. They provide similar symptom control and quality of life compared to conventional talc slurry pleurodesis as confirmed by recent multicenter trials. In addition, IPCs have shown to provide advantages of reduced hospital stay and minimize the need for repeated invasive procedures (AMPLE trial).

Approach to managing the drainage from the catheter varies worldwide. Daily or alternate day drainage (aggressive drainage) is more commonly used in USA, whereas a more symptom-guided approach is common in the rest of the world. Per the ASAP trial, daily drainage promotes pleurodesis more effectively than alternate-day drainage. However, the symptom-guided approach might reduce the risk of iatrogenic infection, burden, and consumable costs compared with daily drainage. Aggressive (daily) versus symptom-guided drainage regimens have not been compared but can have substantial implications on clinical care.

STUDY DESIGN



Type of trial: Randomized, multicenter, open-label trial.

Setting: 11 centers in Australia, New Zealand, Malaysia, and Hong Kong

Randomization: 1:1 to aggressive (daily) or symptom-guided drainage via IPC, by use of an automated telephone-based voice response randomization service.

Randomization was minimized 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)
- prior pleurodesis (vs no prior pleurodesis).

Enrollment Period: July 20, 2015, to Jan 26, 2017

Treatment period and Follow up: 60 days and until 6 months

Primary outcome

Mean daily breathlessness score in the first 60 days after randomization (on 100mm visual analog scale – VAS)

Secondary outcomes

- Rates of spontaneous pleurodesis
- Self-reported global quality-of-life (EQ-5D-5L11,12) after maximal fluid drainage on 100 mm VAS at randomization, 2 weeks, 4 weeks after that monthly for up to 6 months.
- Duration and episodes of hospital stay for any cause (excluding elective admissions for chemotherapy) subdivided into pleural-related (or not) hospital days
- Frequency of adverse events and serious adverse events, and survival

Intervention

- Patients were randomly assigned within 72 hours of IPC insertion after maximum pleural fluid evacuation
- Aggressive group: Drain the IPC daily for the first 60 days unless clinically contraindicated, or till spontaneous pleurodesis occurred.
- Symptom-guided group: Drain when patient had effusion-related symptoms (breathlessness, cough, or chest tightness). IPC was accessed every 14 days to ensure patency and assess fluid production.
- Pleurodesis is defined as:
 - <50 mL of fluid removed at 3 consecutive drainages (in the aggressive drainage group) or
 - < 50 ml of fluid removed on 2 attempts 2 weeks apart (in the symptom-guided group) without substantial residual pleural fluid.
- Drainage regimen after 60 days was left to the discretion of the clinicians.

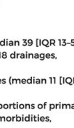
POPULATION

Inclusion criteria

- Adults requiring IPC placement for management of malignant pleural effusion.
- Patients with malignant cells in the pleural fluid/pleural biopsy tissue;
- Large exudative pleural effusion without other causes in a patient with known disseminated extra-pleural malignancy.

Exclusion criteria

- Age < 18 years
- Expected survival < 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
- 1. Inability to consent or comply with the study protocol.



BASELINE CHARACTERISTICS

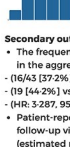
- N = 87: Aggressive:43, Symptom guided: 44

- Aggressive group underwent 1420 drainages (median 39 [IQR 13–57] per participant) for up to 60 days of a possible 1518 drainages, confirming good compliance.

- Symptom-guided group underwent 535 drainages (median 11 [IQR 7–18] per participant) in the same period.

- Both groups were well matched for age, sex, proportions of primary malignancies and trapped lung, effusion size, comorbidities, baseline symptom scores, and ECOG status

OUTCOMES



Primary outcomes:

- Breathlessness scores (100 mm VAS) 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;

Secondary outcomes:

- The frequency of spontaneous pleurodesis was significantly higher in the aggressive drainage group than symptom-guided group.
 - (16/43 [37.2%]) vs (5/44[11.4%], p=0.0049) in first 60 days
 - (19 [44.2%] vs 7 [15.9%], p=0.004) after 6 months
 - (HR: 3.287, 95% CI 1.396–7.740; p=0.0065)
- Patient-reported quality-of-life measures over the study period and follow-up visits were better in the aggressive drainage group (estimated means 0.713 [95% CI 0.647–0.779] vs 0.601 [0.536–0.667]).
- The mean VAS pain score during the first 60 days, time to death at 6 months, total hospital admissions and duration of hospital stay showed no significant difference between the groups
- Patients with trapped lung had a lower rate of pleurodesis than did those with an expandable lung. Aggressive drainage was associated with a higher pleurodesis rate even in the trapped lung group.
- These results were consistent after adjusting for minimization variables

Adverse events:

- 11 patients in the aggressive drainage group and 12 in the symptom-guided drainage group had serious adverse events (SAE).
- 11 episodes of pleural infection developed (5 in the aggressive drainage group and 6 in the symptom-guided drainage group) in 9 patients over 6 months
- Other SAE included:
 - Symptomatic loculation: Aggressive (3), symptom-guided (5)
 - Air leak or pneumothorax: Aggressive (2), symptom-guided(1)
 - Recurrence needing reintervention after IPC removal: Aggressive (1), symptom-guided (1)
 - IPC cellulitis requiring admission: Aggressive (2), symptom-guided (0)
 - IPC blockage requiring admission: Aggressive (0), symptom-guided (1)
 - Worsening dyspnea requiring admission: Aggressive (0), symptom-guided(1)

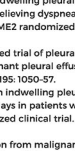
COMMENTARY

This is one of the first randomized controlled trials comparing IPC drainage regimens (aggressive (daily) and the symptom-guided approach). Both approaches provided similar breathlessness control over 60 days after randomization. Pain scores, days spent in the 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 (mobility, self-care, usual activities, discomfort or pain, and anxiety or depression). It confirms the results of ASAP trial that daily indwelling pleural catheter assisted fluid removal enhances spontaneous pleurodesis. This is also one of the very few randomized controlled trials that included patients with a trapped lung, which accounted for a third of the cohort, consistent with commonly quoted data. The study concludes that both approaches are effective in controlling breathlessness and the IPC drainage regimen can be chosen based on the primary aim of IPC insertion (pleurodesis vs. palliation only)

Limitations of this study include that this is an open-label study and use of patient-reported measures could potentially contain bias. The primary endpoint set at 60 days largely represents the short median survival of patients with malignant pleural effusion from lung cancers. Some patients with effusions from mesothelioma have been included and did not show different results. Other malignancies are not well represented. The minimal clinically important difference is not clearly defined for patients with malignant pleural effusion for EQ-5D-5L or VAS quality-of-life scores. This study has provided an approximation of the number of drainage consumables needed for aggressive and symptom-guided drainage. Cost of consumables and care remain variable worldwide and needs further study.

FUNDING

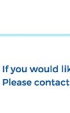
Cancer Council of Western Australia and the Sir Charles Gairdner Research Advisory Group



SUGGESTED READING

1. Davies H, Mishra E, Kahan B, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012; 307: 2383–89.
2. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP trial. Am J Respir Crit Care Med 2017; 195: 1050–57.
3. Thomas R, Fysh ETH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA 2017; 318: 1903–12.
4. Thomas R, Kalomenidis I, Jett J, Lee YCG. Effusion from malignant causes. In: Light RW, Lee YCG, eds. Textbook of pleural diseases, 3rd edn. Boca Raton: CRC Press, Taylor & Francis Group, 2016: 278–94.

ARTICLE CITATION



Muruganandan S, Azzopardi M, Fitzgerald DB, Shrestha R, Kwan BC, Lam DC, De Chaneet CC, Ali MR, Yap E, Tobin CL, Garske LA. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. The Lancet Respiratory Medicine. 2018 Sep 1;6(9):671–80.