AABIP JOURNAL CLUB

# The impact of outpatient versus inpatient management on health-related quality of life outcomes for patients with malignant pleural effusion: the OPTIMUM randomized clinical trial

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## The clinical question

Does outpatient management of symptomatic MPE via IPC and talc pleurodesis improve health related QoL for patients compared to standard inpatient management with chest drainage and talc pleurodesis over 30 days or longer?

## Take Home Message

Outpatient IPC with talc slurry pleurodesis is not superior to inpatient treatment with chest drain and talc slurry pleurodesis in improving global health status measured by a questionnaire (EORTC QLQ-C30) at 30 days; however, both treatment arms sustained improvement in follow up at 60 and 90 days. The IPC pathway was associated with an increased rate of adverse events and failure to achieve pleurodesis. The optimal approach in MPE management for each patient should be based on patient values, preferences, acceptability of risks, social circumstances, affordability and treatment accessibility.

## Background

Prior trials have demonstrated that both interventions have improved dyspnea scores, but no differences between interventions at 30 days.3 In the TIME-2 trial, the improvement in the Visual Analog Score (VAS) between the groups at 6 months favored IPCs.4 For treatment failure as assessed by the need for additional ipsilateral interventions, previous studies have suggested benefits with IPCs over chemical pleurodesis.3,4,5 The two management strategies share the goal of improving patient's healthcare related QoL, but each strategy carries different burdens and logistic considerations. IPC management relies on engagement and support from caretakers and the patients for repeated drainage and healthcare visits, whereas chest drains with talc pleurodesis can prolong hospitalization.

# Study Design

**Type of trial:** open-label randomized controlled trial (RCT)
Two arm, unblinded open-label superiority trial (intention-to-treat)
Patients were randomized 1:1 to either:

- IPC +/- talc slurry pleurodesis (n=70)
- Chest drain + talc slurry pleurodesis (n=72)

**N:** 142 participants with MPE (histocytological confirmation or clinical and radiographic features of metastatic pleural disease with histologically proven cancer)
**Study groups:** patients with symptomatic MPE
**Settings:** UK (11 hospitals), Australia (1 hospital); approved by the UK: National Brighton and Sussex Research Ethics Committee; Australia: Sir Charles Gairdner Group Human Research Ethics Committee
**Enrollment:** 548 patients were screened for eligibility; 142 patients were randomized 1:1 with permuted block randomization with allocation concealment and stratified by: age (<65 or ≥65 years); WHO Performance Status score), malignancy subtype
**Treatment period:** July 2015 – December 2019
**Follow up:** 30-day, 60-day, and 90-day follow up questionnaires. All patients underwent follow up until 90 days after intervention or death, whichever occurred first.
**Primary outcome:** global health status (GHS) measured with the EORTC QLQ-C-30 (European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, 30 items) at 30 days post-intervention
**Statistics:** ANCOVA model adjusted for baseline GHS and sample size of 142 to detect a minimum clinically important difference (MCID) of 8 points (80% power and 5% significance level); interim analysis showed 14% loss to follow up at 30 days but the investigators determined that increasing the sample size would not be feasible (due to barriers in funding, recruitment and the nature of the patient population) and proceeded

# Population

**Inclusion criteria**

- Outpatient and inpatient patients with MPE which was diagnosed with either histocytological confirmation or clinical and radiological features of metastatic pleural disease with histologically proven primary cancers.
- WHO Performance Status ≤ 2 (or PS of 3 expected to improve with pleural drainage)
- Patients with a life expectancy of > 3 months

**Exclusion criteria**

- Age < 18 years
- Underlying lymphoma or small cell carcinoma (unless chemotherapy had failed or the patient was referred for palliation)
- Non-malignant pleural effusions
- Loculated pleural effusions
- Pregnancy or lactation
- Patients with allergies to talc or lidocaine
- Asymptomatic or lack of relief with pleural effusion drainage
- Patients with caregivers/nurses/hospital team unable to carry out at least twice-weekly IPC drainage
- Patients unable to provide written informed consent

**Baseline Characteristics**

Participants were stratified by: age (<65 or ≥65 years); WHO Performance Status score), malignancy subtype

- The ages were similar (IPC group: 69 years vs. chest drain: 66.5)
- There were more females in either group (IPC 54%, chest drain 70%).
- The most common malignancies between both arms were lung, breast, and mesothelioma
- There were comparable rates of treatment between the two arms with patients undergoing chemotherapy and slightly more patients in the IPC group undergoing targeted therapies or immunotherapies
- More patients in the IPC group had larger effusions with >50% of the hemithorax on CXR
- The baseline GHS and VAS breathlessness cores were similar at baseline between the two groups

# Outcomes

**Primary outcomes:** GHS at 30 days post intervention measured with the 30-item EORTC QLQ-C30 (which is a validated cancer specific questionnaire that asks participants to report aspects of their HRQoL over the previous week).

- GHS improved in the day 30 post intervention compared to baseline in both groups:
  - IPC group: mean difference 13.11 (95% CI 5.6-21.1, p=0.001)
  - Chest drain group: mean difference 10.11 (95% CI 4.5-15.7, p=0.001)
- More than half of the patients in each group had >8 point improvement in GHS:
  - IPC group 57% (33/58 patients)
  - Chest drain group 54% (30/56 patients)
- At day 30 (the primary end point) the mean GHS were:
  - IPC group 52.0±24.1
  - chest drain group 50.9±24.1
  - mean difference of 2.06 (95% CI -5.86-9.99, p=0.61)

**Secondary outcomes:** GHS at 60- and 90-day post-intervention

- At 60 days, the mean change in the GHS was:
  - IPC group 15.6±26.4
  - chest drain group 7.96±26.9
  - observed mean difference of 4.82 (95% CI -4.59-14.23, p=0.31)
- At 90 days, the mean change in GHS was:
  - IPC group 13.4±30.6
  - chest drain group 14.93±25.1
  - observed mean difference of -3.12 (95% CI -13.76-7.51, p=0.56)
- Breathlessness scores at 30-, 60- and 90-days with VAS
- Chest pain scores at 30-, 60- and 90-days with VAS
- Pleurodesis failure rate (defined as CXR opacification >25% or the need for subsequent pleural intervention) at 30-, 60- and 90-days post intervention
- IPC arm: 29/65 patients (44.6%) received talc slurry
- Chest drain arm: 49/67 patients (73.1%) received talc slurry
- Incidence of non-expandable lung was similar (< 50% of pleural apposition); IPC group 23% vs. chest drain group 23.9%
- The IPC pleurodesis failure (defined as the IPC remaining in situ, need for subsequent pleural intervention or CXR opacification >25% of the hemithorax) was:
  - 64.3% (18/28) at day 30
  - 64.3% (18/28) at day 60
  - 57.1% (16/28) at day 90
- The chest drain pleurodesis failure (defined as need for subsequent pleural intervention or CXR opacification > 25% of the hemithorax) was:
  - 18.4% (9/49) at day 30
  - 24.5% (12/49) at day 60
  - 26.5% (13/49) at day 90

**Adverse events (AE):**

- There were no intervention related serious AE in the chest drain arm; for the IPC group there were hospital admissions for drain related anxiety (2/83), pain (1/83), pleural infection (1/83), pleurodesis related pain (1/83), pre-pleurodesis steroid withdrawal (1/83) and post-insertion oxygen requirement (1/83)
- For intervention related AE:
- The chest drain group had 13 events including pleurodesis related pain (1/63), hydropneumothorax with air leak (1/63), pleurodesis related fever (1/63), cutaneous infection (2/63), pleural infection (1/63), tube dislodgement (1/63), drain blockage (5/63) and vasovagal syncope during insertion (1/63)
- The IPC arm had 19 events including pleurodesis related pain (1/83), drain related pain (4/83), hydropneumothorax with air leak (2/83), cutaneous infection (5/83), pleural infection (1/83), tube displacement (2/83), drain blockage (2/83), tract metastasis (1/83), and failed drain insertion (1/83)
- Death in the chest drain arm was 20 (n=63) and IPC arm 16 (n=83) with similar rates for admission for symptom control/cancer progression (9 vs 10 patients respectively)

# Commentary

The investigators recognize the main limitation is the data attrition as the study population included a 14% loss to follow up at 30 days but still reported the available data. The population in this study included patients with WHO PS <3 and expected prognosis > 3 months and so results may not be generalizable for patients with MPE who have a worse performance status or shorter life expectancy. Additionally, the EORTC QLQ-C30 questionnaire is validated for cancer populations, but may vary in applicability according to the cancer subtype with prior studies focusing on lung and breast cancer patients. It has not been specifically validated or defined for MPE patients.

The IPC arm had a significantly higher pleurodesis failure rate (69% versus 26.5%) at 90-days post intervention. This could be based off the definition of failure (where patients with the IPC in situ despite successful pleurodesis were considered to have failure as the catheter was not expeditiously removed, CXR opacification greater than 25% on the intervention side as judged by two clinicians or those patients who required a subsequent pleural intervention on the same side as pleurodesis). By this definition, although failure rates were higher, the patients who underwent IPC with an attempt at pleurodesis still reported improved HRQoL. Also, a small group (3/13 patients) preferred to not remove the IPC due to anxiety related to recurrence. Patients in the IPC arm also had larger effusions and were more likely to be receiving corticosteroid therapy during recruitment which may have affected pleurodesis success.

This study may not be applicable to all real-world settings as IPCs require a framework of support and management from patients and caretakers. On the other hand, there are considerations for cost/affordability that must be weighed against hospital resources for inpatient management. There were more reported intervention-related AE in the IPC outpatient treatment arm including hospitalization which may influence the decision making in clinical management of MPE despite the benefits reported here on HRQoL.

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# Suggested Reading

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# Article citation

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# Contributors

***Author***
***Jaskiran Khosa, MD***
*Loma Linda University*

***Reviewer 1:***
***Kai Swenson, MD***
*Beth Israel Deaconess Medical Center*

***Reviewer 2:***
***John P Egan III, MD***
*Michigan State College of Human Medicine/ Corewell Health*

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