# Randomised trial of indwelling pleural catheters for refractory transudative pleural effusions

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**In the first randomised trial on refractory transudative pleural effusions, indwelling pleural catheters did not offer superior control of breathlessness compared to as required therapeutic thoracentesis** https://bit.ly/36mR54x

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## Abstract

***Objective*** Refractory symptomatic transudative pleural effusions are an indication for pleural drainage. There has been supportive observational evidence for the use of indwelling pleural catheters (IPCs) for transudative effusions, but no randomised trials. We aimed to investigate the effect of IPCs on breathlessness in patients with transudative pleural effusions when compared with standard care.

***Methods*** A multicentre randomised controlled trial, in which patients with transudative pleural effusions were randomly assigned to either an IPC (intervention) or therapeutic thoracentesis (TT; standard care). The primary outcome was mean daily breathlessness score over 12 weeks from randomisation.

***Results*** 220 patients were screened from April 2015 to August 2019 across 13 centres, with 33 randomised to intervention (IPC) and 35 to standard care (TT). Underlying aetiology was heart failure in 46 patients, liver failure in 16 and renal failure in six. In primary outcome analysis, the mean±SD breathlessness score over the 12-week study period was 39.7±29.4 mm in the IPC group and 45.0±26.1 mm in the TT group (p=0.67). Secondary outcomes analysis demonstrated that mean±SD drainage was 17 412±17 936 mL and 2901±2416 mL in the IPC and TT groups, respectively. A greater proportion of patients had at least one adverse event in the IPC group (p=0.04).

***Conclusion*** We found no significant difference in breathlessness over 12 weeks between IPCs or TT. TT is associated with fewer complications and IPCs reduced the number of invasive pleural procedures required. Patient preference and circumstances should be considered in selecting the intervention in this cohort.

## Introduction

Transudative pleural effusions are common and while the majority respond to medical optimisation, a proportion will persist and require pleural drainage. Congestive heart failure is the leading cause of pleural effusions, with an estimated annual incidence in the United States of 500 000, with most heart failure patients developing a pleural effusion during their disease course [1, 2]. Liver and renal failure also cause symptomatic effusions, with hepatic hydrothoraces present in up to 10% of patients with advanced cirrhosis [3] and effusions from chronic renal impairment present in a fifth of patients receiving haemodialysis [4].

First-line management of transudative pleural effusions is pharmacological, with diuretics used to reduce dyspnoea [2]. However, high-dose diuretics can cause renal impairment, electrolyte disturbance and postural hypotension, and are not tolerated by some patients. Case series demonstrate that 10% of patients with pleural effusions from heart failure and up to 25% of hepatic hydrothoraces do not respond to medical management [2, 5]. Typically, these patients then undergo repeated therapeutic thoracentesis (TT) to alleviate breathlessness. However, thoracentesis is not without risk as it has been shown that the cumulative risk of complications increases with each subsequent aspiration in patients with hepatic hydrothorax [6].

Refractory transudative effusions, defined in this study as effusions from organ dysfunction, unresponsive to medications and requiring invasive pleural procedures, have been shown in previous studies to have a poor prognosis, with shorter median survival than primary pleural malignancies [7]. There has been little research on definitive management of this patient group, with approaches extrapolated from studies in malignant pleural effusion (MPE). Indwelling pleural catheters (IPCs) have been shown to be an effective treatment in MPE, alleviating dyspnoea and reducing hospitalisation and number of pleural interventions when compared to talc pleurodesis [8, 9]. Observational data suggests that IPCs can reduce breathlessness with low risk of complications in patients with non-MPE [10]. In 2017, IPCs received United States Food and Drug Administration 510(k) clearance for their use in the management of refractory non-MPEs. However, this approval was granted despite a conspicuous paucity of clinical data, with no randomised trials of their use in transudative effusions [11].

This study tests the hypothesis that IPCs are superior to standard care with repeated TT, in management of patients with refractory transudative pleural effusions.

## Methods

### *Trial design*

The REDUCE study was an open-label multicentre randomised controlled trial which was supported by an unrestricted research grant from BD CareFusion (New Jersey, USA). Trial design, implementation, data collection and analysis were performed solely by the trial investigators; the manuscript was written and the decision to submit for publication was made by the authors, without commercial involvement. North Bristol NHS Trust provided trial oversight. Ethics approval for recruitment was obtained from the UK South West – Exeter research ethics committee (REC Reference 14/SW/0075, IRAS project ID 151804). The trial was registered with the International Standard Randomised Clinical Trials Number registry (ISRCTN66354436).

### *Trial setting and participants*

The trial recruited participants from 13 secondary and tertiary care centres in the United Kingdom. Individuals were eligible if they had a symptomatic pleural effusion due to either heart, liver or renal failure, which was either 1) transudative as per the criteria of Light *et al.* [12] or 2) exudative (where malignancy and infection had been confidently excluded as the underlying cause by the treating physician). Key exclusion criteria were life expectancy <3 months, known pleural malignancy, pleural fluid pH <7.2 or an absolute contraindication to IPC insertion, such as skin infection over catheter insertion site or uncorrectable coagulopathy. Patients were assessed by a specialist cardiologist, hepatologist or nephrologist to determine presence of established heart, liver or renal failure and had a symptomatic pleural effusion that persisted despite optimised medical therapy.

### *Randomisation and blinding*

Participants were randomly assigned in a 1:1 ratio to either IPC (intervention) or TT (standard care) using minimisation with a random component of 0.85 [13]. Minimisation factors were 1) underlying aetiology of pleural effusion (heart or renal *versus* liver failure) and 2) size of the effusion on pre-randomisation chest radiograph (⩾½ hemithorax *versus* <½ hemithorax). Heart and renal failure were combined together for minimisation, as they reflect comparable pathogenesis (*i.e.* fluid overload) and its was anticipated the enrolment of renal patients would be low. Conversely, hepatic hydrothorax has a distinct pathogenesis and previous studies have shown outcomes distinct from the other groups [10]. Randomisation was carried out using a central online service. Owing to the nature of the interventions, participants and investigators could not be blinded to treatment allocation. Chest radiograph analysis for secondary outcome measures was performed by assessors blinded to treatment allocation.

### *Study procedures*

Those in the intervention arm had an IPC placed in a hospital procedure room and were discharged for drainage in the community. IPCs were drained at least three times a week for the first 2 weeks, and

subsequently at a frequency considered appropriate by clinicians and patients. Patients receiving standard care had a first TT, removing up to 1.5 L, in a hospital procedure room. In the event of worsening breathlessness, patients were advised to contact the study team, with threshold for contact determined by the patient. Further TTs could then be performed as day-case attendances (elective hospital attendances, typically in a clinic or procedure room not requiring overnight stay) to control symptoms at the treating physician's discretion, with no specification that further frequency of drainage was required. If patients required TT at a frequency deemed unsuitable, then an alternative treatment approach (such as IPC insertion or talc pleurodesis) could be considered at the treating clinician's and patient's discretion.

### Outcomes

All participants were followed-up as outpatients at each recruiting centre at 4, 8 and 12 weeks post-randomisation.

The primary outcome was mean daily breathlessness score over 12 weeks from randomisation, measured using visual analogue scale (VAS) scores (*i.e.* each participant's mean VAS score across all measurement time-points). VAS scores were obtained by asking participants to make a mark on a 100-mm horizontal line (0 mm for "not breathless at all" to 100 mm for "worst possible breathlessness").

Secondary outcome measures included mean daily VAS breathlessness score over 7 and 28 days from randomisation; number of hospital visits, bed days, pleural aspirations, intercostal drain insertions and volume of fluid drained during study period; proportion of patients achieving pleurodesis within 12 weeks of randomisation; quality of life assessed using the EQ-5D-5L questionnaire at 4, 8 and 12 weeks from randomisation; albumin levels at 4, 8 and 12 weeks from randomisation; failure rates of initially randomised treatment; and adverse event and all-cause mortality within study period. Patients were considered to have failed their initial treatment if they underwent a pleural intervention other than that which they were randomised to.

Blood tests (full blood count, renal and liver function) were taken at baseline and at subsequent study visits. Baseline N-terminal pro-brain natriuretic peptide was recorded if available. A chest radiograph was performed during follow-up at the discretion of the primary physician and for all participants at the 12-week assessment to establish whether pleurodesis had occurred.

For the IPC group, pleurodesis was defined as chest radiograph showing an effusion less than a third of the total hemithorax on the side of the effusion initially randomised as agreed by two independent assessors blinded to treatment, with <50 mL aspirated from the IPC on three occasions over $\geqslant$1 week with a patent IPC, or the IPC was removed, and no further pleural intervention required within the study period. In the TT group, pleurodesis was defined as chest radiograph showing an effusion less than a third of the total hemithorax on the side of the effusion initially randomised as agreed by two independent assessors blinded to treatment, with no further pleural fluid intervention since the initial aspiration.

### Statistical analysis

To address the primary objective, we required 86 patients to have 80% power to detect a 7-mm difference in means between groups at the 5% level, assuming a standard deviation of 11 mm, and allowing for 8% loss to follow-up. A difference of 7 mm was chosen from pilot data, described in the supplementary statistical analysis plan.

All analyses were conducted according to intention-to-treat principle [14]. All analyses adjusted for the minimisation variables (cause of effusion and size of effusion) [15]. The primary outcome of daily breathless score was analysed using a mixed-effects linear regression model, which included treatment allocation, study day, the minimisation variables and the breathless score at baseline as fixed factors [16]. Study day was included using restricted cubic splines with three knots; breathless score at baseline was included assuming a linear associated with the outcome [17]. Missing values of baseline breathlessness were imputed using mean imputation [18]. The model included a random intercept for patient, used an autoregressive (order 1) correlation, and was estimated using restricted maximum likelihood with a Kenward–Roger degree-of-freedom correction [19]. This model is valid even when some participants have days with missing VAS scores, under the missing-at-random assumption; this is achieved through the use of a random intercept in conjunction with an autoregressive correlation structure, which models the correlation between VAS scores on different days within the same participant. This correlation structure allows the correlation to decrease over time, but never to approach 0. The number of hospital visits, bed days, pleural aspirations and intercostal drain insertions were all analysed using a negative binomial regression model, while the number achieving pleurodesis, failure of initially randomised treatment,

number experiencing at least one adverse event and all-cause mortality were all analysed using a logistic regression model.

Subgroup analyses were performed for the primary outcome by cause of effusion and size of effusion and were performed for the outcome albumin at 12 weeks according to the cause of effusion. All analyses were performed using Stata 16.1. Further details on the statistical methods used to implement analyses are available in the supplementary statistical analysis plan.

## Results

### *Recruitment and population characteristics*

Recruitment and follow-up of the participants took place from April 2015 to December 2019. Over this period, 220 potential participants were identified. 68 patients were randomised, 33 to IPC (of whom 31 had an IPC inserted) and 35 to TT (all of whom received TT) (figure 1). The study did not reach the target sample size of 86 in the pre-defined study period due to slower than anticipated recruitment, with sponsor decision not to extend the recruitment period. In total, four (12%) out of 33 IPC patients withdrew. One withdrawal was due to cognitive deterioration and three withdrawals were due to patient preference; one patient had difficulty sleeping following IPC insertion and two withdrew after IPC removal (one accidental, one after IPC-related pleurodesis). By contrast, none of 35 patients receiving standard care withdrew from the study. The two study groups were generally well matched at baseline (table 1). The baseline characteristics by aetiology are shown in table 2.

### *Primary outcome*

There was no significant difference between treatments in the primary outcome analysis, with mean±SD breathless score over the 12-week study period of 39.7±29.4 mm in the IPC arm and 45.0±26.1 mm in the TT arm (mean difference −2.9 mm, 95% CI −16.1–10.3; p=0.67) (figure 2).

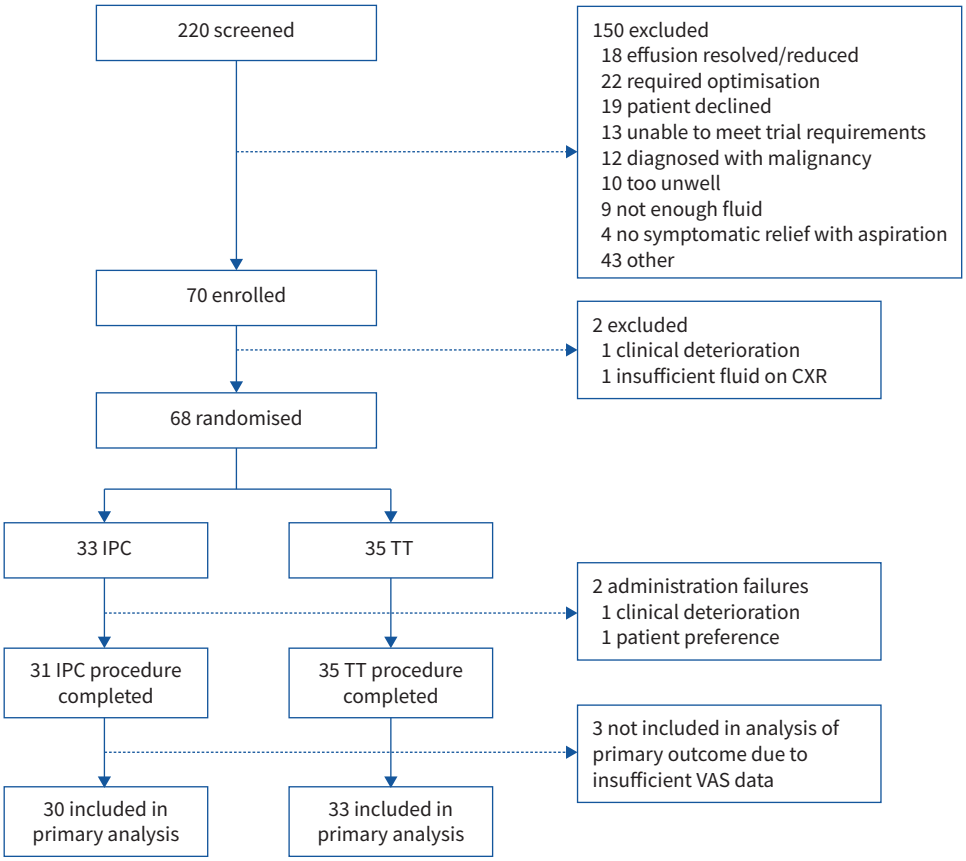


**FIGURE 1** Consolidated Standards of Reporting Trials diagram detailing identification, recruitment, randomisation and follow-up of study participants. CXR: chest radiograph; IPC: indwelling pleural catheter; TT: therapeutic thoracentesis; VAS: visual analogue scale.

**TABLE 1** Baseline characteristics by treatment group

| | TT group | IPC group |
|---|---|---|
| **Patients** | 35 | 33 |
| **Age (years)** | 73.6±12.1 | 73.2±12.0 |
| **Female** | 9 (26) | 6 (18) |
| **Primary cause of effusion** | | |
| Heart failure | 25 (71) | 21 (64) |
| Liver failure | 8 (23) | 8 (24) |
| Renal failure | 2 (6) | 4 (12) |
| **Size of effusion** | | |
| >1/2 hemithorax | 12 (34) | 14 (42) |
| **Smoking status** | | |
| Never-smoker | 13 (37) | 16 (48) |
| Ex-smoker | 20 (57) | 16 (48) |
| Current smoker | 2 (6) | 1 (3) |
| **WHO performance status** | | |
| 0 | 0 (0) | 1 (3) |
| 1 | 14 (40) | 10 (30) |
| 2 | 16 (46) | 12 (36) |
| 3 | 5 (14) | 9 (27) |
| 4 | 0 (0) | 1 (3) |
| **Side of effusion requiring intervention** | | |
| Right | 28 (80) | 26 (79) |
| **Previous pleural intervention on same side of effusion in previous 3 months** | 26 (74) | 25 (76) |
| **Duration of symptoms** | | |
| <1 month | 2 (6) | 3 (9) |
| 1–3 months | 5 (14) | 6 (18) |
| 3–6 months | 9 (26) | 10 (30) |
| >6 months | 19 (54) | 14 (42) |
| **Total volume of pleural fluid drained in previous 3 months (mL)** | 1950 (875–3225) | 1790 (1000–4550) |
| **Receiving anticoagulation** | 18 (51) | 19 (58) |
| **Receiving clopidogrel** | 3 (9) | 2 (6) |
| **Albumin ($g \cdot L^{-1}$)** | 31.8±4.8 | 31.1±10.5 |
| **Breathlessness (VAS)** | 57±29 | 46±24 |

Data are presented as n, mean±SD, n (%) or median (interquartile range). TT: therapeutic thoracentesis; IPC: indwelling pleural catheter; WHO: World Health Organization; VAS: visual analogue scale.

### *Subgroup analysis of primary outcome*

Subgroup analysis did not show any significant differences in treatment effects between different causes of effusion (heart/renal *versus* liver) or size of effusion (⩾½ or <½ hemithorax) (table 3).

### *Secondary outcomes*

There was no significant difference between treatments in mean breathlessness scores over the first 7 or 28 days (table 4). *Post hoc* analysis demonstrated gradual improvement in breathlessness within the IPC arm and static breathlessness scores in the TT arm (table 5). However, there were no significant differences between the treatment arms over the first, second and third months (table 5).

There was no difference in mean number of bed days, care visits or pleurodesis success rates during the study period (table 4). Baseline EQ-5D index was 0.57 (interquartile range (IQR) 0.33–0.74) and EQ-5D VAS was 50 mm (35–70 mm) in the IPC group and 0.58 mm (0.33–0.68 mm) and 50 mm (40–70 mm) in the TT group. There was no statistical difference in EQ-5D scores between groups at baseline or at the subsequent monthly visits.

The TT group required 1.3±1.4 additional TT during the study period, with no additional TT required in the IPC group. The mean±SD drainage volume during the study period was 17412±17936 mL and 2901±2416 mL in the IPC and TT group, respectively (difference 13892 mL, 95% CI 7669–20116 mL; p<0.001). In the TT group, 17% (six out of 35) failed their initially randomised treatment, compared to none out of 33 in the IPC group. In the TT group three (9%) patients required a chest drain, one of whom

**TABLE 2** Baseline characteristics by aetiology

| | TT group | | IPC | |
|---|---|---|---|---|
| | Patients with available data | TT | Patients with available data | IPC |
| **Patients** | 35 | | 33 | |
| **Heart failure patients (n=46)** | | | | |
| Cardiac diagnosis | 25/25 (100) | | 21/21 (100) | |
| Ischaemic heart disease | | 8 (32) | | 10 (48) |
| Atrial fibrillation | | 19 (76) | | 10 (48) |
| Valvular heart disease | | 3 (12) | | 5 (24) |
| Cardiac amyloid | | 0 (0) | | 1 (5) |
| Total daily loop-diuretic dose[#] (mg) | 25/25 (100) | 87±53 | 21/21 (100) | 107±103 |
| Total daily spironolactone (mg) | 25/25 (100) | 9±20 | 21/21 (100) | 4±9 |
| NT-proBNP (pg·mL$^{-1}$) | 11/25 (44) | 7801±11 757 | 4/21 (19) | 8812±3829 |
| **Liver failure patients (n=16)** | | | | |
| Total daily loop-diuretic dose[#] (mg) | 8/8 (100) | 28±28 | 8/8 (100) | 20±30 |
| Total daily spironolactone (mg) | 8/8 (100) | 125±117 | 8/8 (100) | 75±117 |
| MELD score | 7/8 (88) | 16±6 | 8/8 (100) | 15±7 |
| **Renal failure patients (n=6)** | | | | |
| Total daily loop-diuretic dose[#] (mg) | 2/2 (100) | 125±177 | 4/4 (100) | 60±77 |
| Haemodialysis | 2/2 (100) | 2 (100) | 4/4 (100) | 3 (75) |
| Peritoneal dialysis | 2/2 (100) | 0 (0) | 4/4 (100) | 1 (25) |

Data are presented as n, n (%) or mean±SD. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter; NT-proBNP: N-terminal pro-brain natriuretic peptide; MELD: Model for End-Stage Liver Disease. [#]: combined daily diuretic dose of furosemide or bumetanide (at 40 mg=1 mg equivalence).

also had talc slurry pleurodesis. Two (6%) patients randomised to TT had an IPC subsequently sited to manage their symptoms. One (3%) patient in the TT group had a medical thoracoscopy, with 3300 mL drained at procedure. No patients in the IPC group required a further invasive pleural procedure due to

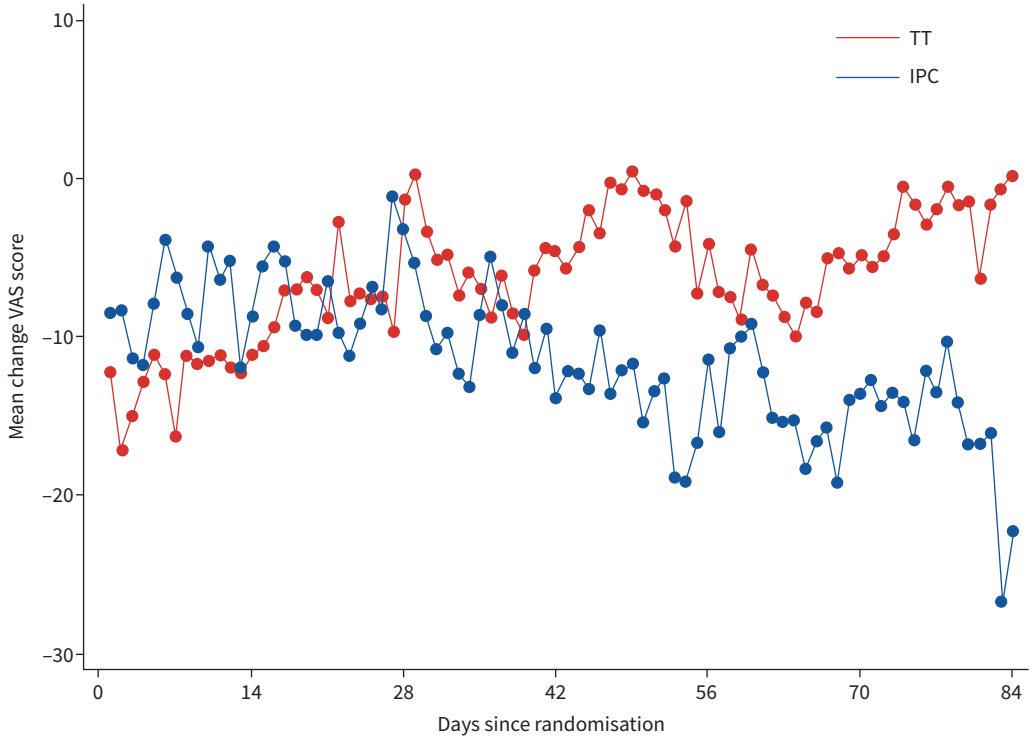


**FIGURE 2** Change from baseline in daily mean visual analogue scale (VAS) score over the 12-week study period. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter.

**TABLE 3** Primary outcomes for pre-defined subgroup analysis

| | TT group | | IPC group | | Treatment effect estimate (95% CI) | p-value for interaction |
|---|---|---|---|---|---|---|
| | Patients with available data | Breathlessness (VAS) over 12 weeks | Patients with available data | Breathlessness (VAS) over 12 weeks | | |
| **Patients** | | 35 | | 31 | | |
| **Cause of effusion** | | | | | | |
| Heart/renal failure | 26/27 (96) | 48.5±24.6 | 22/25 (88) | 40.7±27.5 | −4.5 (−19.2–10.2) | 0.62 |
| Liver failure | 7/8 (88) | 32.3±29.1 | 8/8 (100) | 36.8±36.2 | 3.2 (−23.4–29.7) | |
| **Size of effusion** | | | | | | |
| <½ hemithorax | 21/23 (91) | 49.1±24.4 | 16/19 (84) | 48.9±31.3 | −0.6 (−17.3–16.2) | 0.67 |
| ⩾½ hemithorax | 12/12 (100) | 38.0±28.5 | 14/14 (100) | 29.1±24.0 | −6.2 (−26.4–14.0) | |

Data are presented as n, n (%) or mean±SD, unless otherwise stated. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter; VAS: visual analogue scale.

failure of their initially randomised treatment, although one patient required their IPC re-sited due to device malfunction.

The serum albumin level at 12 weeks was 27.0±7.5 $g \cdot L^{-1}$ and 32.5±5.1 $g \cdot L^{-1}$ in the IPC and TT cohorts (p-value <0.001) (table 4). Subgroup analysis for albumin levels for heart/renal failure patients at 12 weeks was 28.0±6.7 $g \cdot L^{-1}$ for the IPC group and 33.2±5.3 $g \cdot L^{-1}$ for the TT group. Albumin levels for hepatic

**TABLE 4** Secondary outcomes

| | TT group | | IPC group | | Treatment effect (IPC *versus* TT) and 95% CI | p-value |
|---|---|---|---|---|---|---|
| | Patients with available data | TT group | Patients with available data | IPC group | | |
| **Patients** | 35 | | 31 | | | |
| **Breathlessness (VAS) over the first 7 days** | 27 (77) | 41.3±25.4 | 25 (76) | 38.5±22.3 | 1.4 (−11.9–14.8) | 0.83 |
| **Breathlessness (VAS) over the first 28 days** | 31 (89) | 44.3±23.5 | 27 (82) | 37.8±26.0 | −2.9 (−15.1–9.3) | 0.63 |
| **Pleurodesis success within 12 weeks** | 32 (91) | 2/32 (6) | 24 (73) | 3/24 (13) | 2.59 (0.38–17.72) | 0.33 |
| **Volume of fluid drained within 12 weeks of randomisation** | 34 (97) | 2901±2416 | 31 (94) | 17 412±17 936 | 13 892 (7669–20 116) | <0.001 |
| **Total number of hospital bed days within 12 weeks of randomisation** | 35 (100) | 3.7±9.0 | 31 (94) | 1.3±3.5 | 0.21 (0.02–2.22) | 0.20 |
| **Number of hospital visits within 12 weeks of randomisation** | 35 (100) | 1.8±3.4 | 31 (94) | 2.4±4.0 | 1.13 (0.55–2.32) | 0.74 |
| **Number of TT within 12 weeks of randomisation** | 35 (100) | 1.3±1.4 | 31 (94) | 0 | NA | NA |
| **Number of intercostal drain insertions within 12 weeks of randomisation** | 35 (100) | 0.1±0.3 | 31 (94) | 0 | NA | NA |
| **Failure of initially randomised treatment within 12 weeks of randomisation** | 35 (100) | 6/35 (17) | 31 (94) | 0/31 (0) | NA | NA |
| **At least one adverse event within 12 weeks of randomisation** | 35 (100) | 13/35 (37) | 31 (94) | 19/31 (59) | 3.13 (1.07–9.13) | 0.04 |
| **All-cause mortality within 12 weeks of randomisation** | 35 (100) | 2/35 (6) | 31 (94) | 5/31 (16) | 3.80 (0.65–22.15) | 0.14 |
| **Serum albumin level ($g \cdot L^{-1}$)** | 34 (97) | | 29 (88) | | | |
| At 4 weeks | | 33.1±4.3 | | 27.1±5.2 | −5.1 (−7.1– −3.1) | <0.001 |
| At 8 weeks | | 31.9±4.0 | | 27.9±6.1 | −4.5 (−6.7– −2.2) | <0.001 |
| At 12 weeks | | 32.5±5.1 | | 27.0±7.5 | −5.7 (−8.9– −2.6) | <0.001 |

Data are presented as n, n (%) or mean±SD, unless otherwise stated. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter; VAS: visual analogue scale; NA: not applicable.

**TABLE 5** *Post hoc* analysis of mean monthly breathlessness (visual analogue scale (VAS))

| | Number included in analysis | | Mean breathlessness (VAS) | | Treatment effect (IPC *versus* standard care) and 95% CI | p-value |
|---|---|---|---|---|---|---|
| | TT group | IPC group | TT group | IPC group | | |
| **Days 1–28** | 31 (89) | 27 (82) | 44.3±23.5 | 37.8±26.0 | −2.9 (−15.1–9.2) | 0.63 |
| **Days 29–56** | 32 (91) | 27 (82) | 45.9±28.4 | 40.5±30.9 | −1.0 (−16.2–14.1) | 0.89 |
| **Days 57–84** | 31 (89) | 22 (67) | 45.8±28.5 | 31.5±30.2 | −8.5 (−25.3–8.3) | 0.31 |

Data are presented as n (%) or mean±SD, unless otherwise stated. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter.

hydrothorax patients at 12 weeks were 24.7±9.1 $g \cdot L^{-1}$ for the IPC group and 29.8±2.9 $g \cdot L^{-1}$ for the TT group (p-value for interaction=0.83). Seven (88%) out of the eight patients with hepatic hydrothorax received 20% human albumin solution (HAS) at the treating physician's discretion.

### *Adverse events*

In total, 59% (19 out of 32) of the patients in the IPC arm had at least one adverse event, compared to 37% (13 out of 35) managed with TT (OR 3.13, 95% CI 1.07–9.13; p=0.04). There were 39 adverse events in the IPC arm and 24 in the TT group (table 6). In the IPC group there were 12 serious adverse events (SAEs), defined as medical occurrences that resulted in death, were life threatening, required prolonged hospitalisation or resulted in significant disability or incapacity. Eight adverse events were felt to be secondary to IPC insertion, including leakage from the IPC wound site, significant pain after IPC insertion, IPC malfunction, nondrainage due to pleural septations and self-resolving localised swelling at the IPC insertion site. In one instance the one-way valve became disconnected from the IPC, with resultant fluid leakage and a need to replace the IPC. There was one case of IPC site cellulitis which progressed to IPC-related pleural infection and necessitated hospital admission for intravenous antibiotics. The patient died of end-stage heart failure and acute kidney injury, with pleural infection a contributory cause. Four other patients with an IPC died, one with end-stage heart failure, one with liver failure and acute kidney injury, one with renal transplant failure and one with end-stage renal disease. In the TT group there were seven SAEs, with three adverse events (all pneumothoraces) secondary to TT. One of these was classified as iatrogenic, one as trapped lung and one as a spontaneous pneumothorax. Two patients managed with TT died. The first was electively hospitalised for fluid management, then developed hepatic encephalopathy and hypercapnic respiratory failure with subsequent deterioration. The second was hospitalised with

**TABLE 6** Adverse events

| | TT group | IPC group | Total |
|---|---|---|---|
| **Patients** | 35 | 33 | 68 |
| **Device- and procedure-related** | | | |
| Fluid leakage from IPC | 0 | 2 | 2 |
| Device malfunction | 0 | 1 | 1 |
| Nondrainage | 0 | 1 | 1 |
| Localised swelling (noninfected) | 0 | 1 | 1 |
| Pneumothorax | 3 | 0 | 3 |
| Adverse reaction to talc pleurodesis | 1 | 0 | 1 |
| Chest pain | 0 | 4 | 4 |
| **Infection** | | | |
| Pleural infection | 0 | 1 | 1 |
| Localised peri-device cellulitis | 0 | 1 | 1 |
| Chest infection | 4 | 3 | 7 |
| Cellulitis (nonthoracic) | 0 | 2 | 2 |
| Infection (other, nonrelated) | 1 | 2 | 3 |
| **Admission secondary to decompensation of underlying disease** | 9 | 9 | 18 |
| **Acute kidney injury** | 2 | 2 | 4 |
| **Other adverse event, not related to study intervention** | 4 | 10 | 14 |
| **Total** | 24 | 39 | 63 |

Data are presented as n. TT: therapeutic thoracentesis; IPC: indwelling pleural catheter.

dyspnoea and developed hypercapnic respiratory failure on a background of heart failure and acute kidney injury.

## Discussion

This is the first randomised controlled trial of the use of IPCs in patients with pleural effusions secondary to heart, liver or renal failure. We found no difference in mean breathlessness scores, as assessed by daily VAS, between the use of IPCs and as required TT over a 12-week study period.

Previous nonrandomised studies have demonstrated improvements in dyspnoea with IPCs in transudative effusions, with both Srour *et al.* [20] and Potechin *et al.* [21] reporting an improvement at 2 weeks using a baseline and transitional dyspnoea index score in cardiac- and renal-related effusions, respectively, and other observational studies reporting high rates of symptom improvement with IPC in nonmalignant effusions [22, 23]. This supports the rationale that the frequent drainages offered by the IPC leads to sustained symptom relief. While in this study there appears to be gradual improvement in the daily mean breathlessness in the IPC group, it was not shown to be superior when compared to TT. This is despite large differences in the drainage volumes between the groups, with the IPC group draining, on average, six times greater fluid volume than those managed with TT.

That increased drainage volumes did not translate to lower symptoms scores suggests that the cause of breathlessness in these patients is multifactorial and not solely related to pleural fluid volume. Alternatively, removal of pleural fluid, without correction of the underlying abnormal oncotic pressure gradients, may lead to short-term benefits in breathing, but may ultimately precipitate pleural fluid re-accumulation [24].

An alternative explanation of the failure to reject the null hypothesis is that the trial did not achieve its intended recruitment target. However, with the trial achieving >80% target recruitment and with small intergroup differences between VAS breathlessness, it is unlikely that a larger study would have demonstrated a clinically meaningful difference.

Overall, patients in both study groups had very poor health status, with lower mean quality-of-life scores than in studies of patients with primary pleural malignancies [25]. This is the first study to demonstrate the extent of the symptom burden in this patient group. The choice of intervention in this study did not affect quality-of-life scores between treatment groups.

Patients managed with IPCs underwent fewer additional invasive pleural procedures, with six patients in the TT cohort undergoing chest tube insertion to manage their dyspnoea, including two IPCs and one thoracoscopic procedure. However, the average number of repeated aspirations required in this group was low, with just under half not requiring a further aspiration. It is unclear why this was the case, with a high persistent mean breathlessness score in the group, and a moderate-to-large effusion in nearly a third at the end of the study. Whether this reflects a reluctance of medical staff to aspirate a transudative effusion, lack of perceived benefit, access barriers to day-case appointments, or patient preference is unclear. Over half the patients were taking anticoagulants, which may have influenced decisions regarding repeat aspirations.

IPCs were associated with higher rates of adverse events. Most of these had minimal impact on the patient and the risk of infective complications was low. Risk of IPC-related infection is a commonly cited concern in nonmalignant effusions, although pooled analysis of previous rates has shown low rates of 2% [26]. Concern about infection is particularly high for patients with end-stage liver disease, who have associated immunosuppression, thrombocytopenia and coagulopathy [27]. Specifically, for hepatic hydrothorax there is concern that infective complications could delay or exclude potential eligible patients from liver transplantation [28]. This concern has been amplified by high rates of infection in IPC in series of nonrandomised and predominantly retrospective studies of cirrhotic patients, which demonstrate rates between 10% and 25% [29–32]. Reassuringly, in our study there was only one case of IPC-related infection and none in the hepatic hydrothorax cohort.

An additional concern with use of IPC in transudative effusions, particularly hepatic hydrothorax, is that repeated large-volume drainage may cause nutritional or electrolyte derangement. An earlier study of IPCs in patients with hepatic hydrothorax demonstrated a small downward trend of serum albumin of $0.3\ g{\cdot}dL^{-1}$, of uncertain clinical significance [30]. In our study, there was a decline of serum albumin levels in patients with an IPC which was not evident in patients managed with TT. It occurred in both heart failure and liver failure groups, though the decrease was greater with liver patients. The clinical significance of this decrease in albumin levels is uncertain and the role of *i.v.* HAS in this cohort is

unestablished, with it being mainly used during ascitic drainages to prevent paracentesis-induced circulatory dysfunction (PICD), which is associated with worsening renal function, ascites re-accumulation and poorer prognosis [33]. However, HAS has only been shown to reduce rates of PICD when the drainages volumes >6 L, which is unlikely in a single IPC drainage [34]. Further research is needed to examine to role of HAS in IPC drainage of hepatic hydrothorax.

Patient selection may influence treatment response to pleural intervention, with patients whose effusions rapidly and repeatedly re-accumulate likely to benefit from IPCs the most. However, there are no validated predictive models to determine which transudative effusions will be refractory and to what degree. Our study found no difference in treatment effect regardless of underlying aetiology or size of effusion.

This study is limited by modest under-recruitment and may not be powered to detect a small difference in VAS score. Even though the study is underpowered, the primary analysis can serve to rule out extremely large differences in treatment effect for either intervention and this trial provides extra data on safety and secondary outcomes, which were unknown before. Many participants had days with missing VAS scores for the primary outcome, particularly towards the end of follow-up. We used an analysis method which accounts for such missing data under a missing-at-random assumption. If data are missing-not-at-random (*e.g.* participants with particularly poor outcomes are more likely to have missing data) then this analysis method may produce biased estimates of treatment effect; however, sensitivity analyses found that results were consistent even under different missing-not-at-random assumptions, except when participants with missing data were assumed to have extremely high or extremely low VAS scores. It was not feasible to blind study participants and clinicians to study intervention, although this was to some extent mitigated by blinded outcome assessment.

### *Conclusion*

In this study, IPCs did not offer greater control of breathlessness than repeated TT for recurrent nonmalignant effusion, despite large difference in drainage volumes. This may represent a failure to correct the underlying abnormal physiology in patients with severe end-organ disease. Repeated TT had fewer complications and maintained albumin levels. However, patients managed with IPCs underwent on average, fewer invasive pleural procedures, with infrequent serious complications, in a population in whom over half were on long-term anticoagulation therapy. Patient preference and circumstances should be considered in selecting the intervention in this cohort. IPC may have a role in selected patients who do not tolerate repeated TT, prefer a treatment strategy deliverable at home or in whom repeated interruption of anticoagulant therapy is undesirable.

This study is a clinical trial registered as ISRCTN66354436. Individual de-identified participant data (including data dictionaries) will be shared. Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures and appendices) will be shared in particular. Study protocol and statistical analysis plan are the other documents available. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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## References

1 Light RW. Pleural effusions. *Med Clin North Am* 2011; 95: 1055–1070.
2 Kataoka H. Pericardial and pleural effusions in decompensated chronic heart failure. *Am Heart J* 2000; 139: 918–923.
3 Alberts WM, Salem AJ, Solomon DA, *et al.* Hepatic hydrothorax: cause and management. *Arch Intern Med* 1991; 151: 2383–2388.
4 Bakirci T, Sasak G, Ozturk S, *et al.* Pleural effusion in long-term hemodialysis patients. *Transplant Proc* 2007; 39: 889–891.
5 Porcel JM. Management of refractory hepatic hydrothorax. *Curr Opin Pulm Med* 2014; 20: 352–357.

6 Shojaee S, Khalid M, Kallingal G, *et al.* Repeat thoracentesis in hepatic hydrothorax and non-hepatic hydrothorax effusions: a case-control study. *Respiration* 2018; 96: 330–337.
7 Walker SP, Morley AJ, Stadon L, *et al.* Non-malignant pleural effusions: a prospective study of 356 consecutive unselected patients. *Chest* 2017; 151: 1099–1105.
8 Davies HE, Mishra EK, Kahan BC, *et al.* Effect of an indwelling pleural catheter *vs* chest tube and talc pleurodesis for relieving dyspnoea in patients with malignant pleural effusion: the TIME2 randomised controlled trial. *JAMA* 2012; 307: 2383–2389.
9 Thomas R, Fysh ET, 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: 1903–1912.
10 Patil M, Dhillon SS, Attwood K, *et al.* Management of benign pleural effusions using indwelling pleural catheters: a systematic review and meta-analysis. *Chest* 2017; 151: 626–635.
11 Aboudara M, Maldonado F. Indwelling pleural catheters for benign pleural effusions: what is the evidence? *Curr Opin Pulm Med* 2019; 25: 369–373.
12 Light RW, Macgregor MI, Luchsinger PC, *et al.* Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; 77: 507–513.
13 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975, 31: 103–115.
14 White IR, Horton NJ, Carpenter J, *et al.* Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011; 342: d40.
15 Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med* 2012; 31: 328–340.
16 Kahan BC, Jairath V, Doré CJ, *et al.* The risks and rewards of covariate adjustment in randomised trials: an assessment of 12 outcomes from 8 studies. *Trials* 2014; 15: 139.
17 Kahan BC, Rushton H, Morris TP, *et al.* A comparison of methods to adjust for continuous covariates in the analysis of randomised trials. *BMC Med Res Methodol* 2016; 16: 42.
18 White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomised trials. *Stat Med* 2005; 24: 993–1007.
19 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997; 53: 983–997.
20 Srour N, Potechin R, Amjadi K. Use of indwelling pleural catheters for cardiogenic pleural effusions. *Chest* 2013; 144: 1603–1608.
21 Potechin R, Amjadi K, Srour N. Indwelling pleural catheters for pleural effusions associated with end-stage renal disease: a case series. *Ther Adv Respir Dis* 2015; 9: 22–27.
22 Mullon J, Maldonado F. Use of tunneled indwelling pleural catheters for palliation of nonmalignant pleural effusions. *Chest* 2011; 140: 996A.
23 Parsaei N, Khodaverdian R, McKelvey AA, *et al.* Use of long-term indwelling tunneled pleural catheter for the management of benign pleural effusion. *Chest* 2006; 130: 271S.
24 Estenne M, Yernault JC, De Troyer A. Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions. *Am J Med* 1983; 74: 813–819.
25 Arnold D, Hooper C, Morley A, *et al.* The effect of chemotherapy on health-related quality of life in mesothelioma: results from the SWAMP trial. *Br J Cancer* 2015; 112: 1183–1189.
26 Patil M, Dhillon SS, Attwood K, *et al.* Management of benign pleural effusions using indwelling pleural catheters: a systematic review and meta-analysis. *Chest* 2017; 151: 626–635.
27 Walker S, Shojaee S. Nonmalignant pleural effusions: are they as benign as we think? In: Maskell NA, Laursen CB, Lee YCG, *et al.* eds. Pleural Disease (ERS Monograph). Sheffield, ERS, 2020; pp. 218–231.
28 Walker S, Maldonado F. Indwelling pleural catheter for refractory hepatic hydrothorax: the evidence is still fluid. *Chest* 2019; 155: 251–253.
29 Shojaee S, Rahman N, Haas K, *et al.* Indwelling tunneled pleural catheters for refractory hepatic hydrothorax in patients with cirrhosis: a multicenter study. *Chest* 2019; 155: 546–553.
30 Kniese C, Diab K, Ghabril M, *et al.* Indwelling pleural catheters in hepatic hydrothorax: a single-center series of outcomes and complications. *Chest* 2019; 155: 307–314.
31 Chen A, Massoni J, Jung D, *et al.* Indwelling tunneled pleural catheters for the management of hepatic hydrothorax. A pilot study. *Ann Am Thorac Soc* 2016; 13: 862–866.
32 Kilburn JP, Hutchings J, Misselhorn D, *et al.* Use of indwelling tunneled pleural catheters for the management of hepatic hydrothorax. *Chest* 2010; 138: 418A.
33 Ginès P, Titó L, Arroyo V, *et al.* Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988; 94: 1493–1502.
34 Moreau R, Valla DC, Durand-Zaleski I, *et al.* Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trial. *Liver Int* 2006; 26: 46–54.