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Peer reviewed version

Link to published version (if available):
10.1183/13993003.01362-2021

Randomised Trial of Indwelling Pleural Catheters for Refractory Transudative Pleural Effusions

Introduction

Transudative pleural effusions are common and whilst the majority respond to medical optimisation, a proportion will persist and require pleural drainage. Congestive heart failure (CHF) is the leading cause of pleural effusions, with an estimated annual incidence in the US 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 (HH) present in up to 10% of patients with advanced cirrhosis(3) and effusions from renal impairment present in a fifth of patients receiving haemodialysis(4).

The 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 HH 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; it has been shown in patients with HH that the cumulative risk of complications increases with each subsequent aspiration (6).

Refractory transudative effusions have been shown in previous studies to have a poor prognosis, with median survival poorer than primary pleural malignancies(7). Accordingly, alleviating symptoms while minimising length of hospitalisation and number of invasive

procedures is the management goal. 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 hospitalization and number of pleural interventions when compared to talc pleurodesis(8, 9). In 2017, IPCs received US 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 (10).

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 trial was an open-label multi-centre randomised controlled trial which was supported by an unrestricted research grant from BD CareFusion (New Jersey, USA), who supplied IPCs and drainage bottles for all participants. 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 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 diagnosis of symptomatic pleural effusion secondary to either heart, liver or renal failure, with an aspirate demonstrating a transudate by Light's criteria(11). Patients with exudative effusions could be included, where malignancy and infection had been confidently excluded as a cause by the treating physician. Key exclusion criteria were life expectancy less than 3 months, known pleural malignancy, pleural fluid pH <7.2, or an absolute contraindication to IPC insertion.

Randomization and Blinding

Participants were randomly assigned in a 1:1 ratio to either an IPC (intervention) or a TT (standard care) using minimisation with a random component of 0.85(12). Minimisation

factors were underlying aetiology of pleural effusion (heart/renal vs liver failure) and size of the effusion on pre-randomisation chest radiograph (≥½ hemithorax vs <½ hemithorax). 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 two weeks, and subsequently at a frequency considered appropriate by clinicians and patients. Patients receiving standard care had a first TT, removing up to 1.5L in a hospital procedure room. Further TTs could be performed as day-case attendances to control symptoms at the treating physician's discretion, with no specification that further frequency of drainage was required.

All participants were followed up as outpatients at each recruiting centre at four, eight and twelve weeks. At each visit, assessments included completion of the EuroQoL Group 5-Dimensions 5-Level (EQ-5D-5L) questionnaire and a clinical assessment. During follow-up a chest radiograph was performed at the discretion of the primary physician and for all participants at the 12-week assessment to establish if pleurodesis had occurred.

Primary Outcome

The primary outcome was mean daily breathlessness score over 12 weeks from randomisation, measured using VAS scores. The VAS breathlessness consists of a 100mm horizontal line, 0mm for 'not breathless at all' to 100mm for 'worst possible breathlessness'.

Secondary outcome measures included: mean daily 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; adverse event and all-cause mortality within study period.

Statistical analysis

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

All analyses were conducted according to intention-to-treat principle (13). All analyses adjusted for the minimisation variables (cause of effusion and size of effusion)(14). The primary outcome of daily breathless score was analysed using a mixed-effects linear regression model (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). Missing values of baseline breathlessness were imputed using mean imputation(17). 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(18). 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 statistical analysis plan.

Results

Recruitment and Population Characteristics

Recruitment and follow-up of the participants took place over a period of 4 years, from April 2015 to December 2019. There were 220 potential participants, with 68 patients randomised, 33 to IPC (intervention) of whom 31 had an IPC inserted and 35 to TT (standard care) 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 recruitment period.

In total 4/33 (12%) IPC patients withdrew, with one withdrawal 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 (on accidental, one after IPC-related pleurodesis). By contrast, none of 35 receiving standard care withdrew.

Primary outcome

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

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 (less or greater/equal than hemithorax) (table 2).

Secondary outcomes

There was no significant difference between treatments in mean breathless scores over the first 7 or 28 days (table 3). Post hoc analysis demonstrated gradual improvement in breathlessness within the IPC arm and static breathlessness scores in the TT arm (table 4). There were, however, no significant differences between the treatment arms over the first, second and third month (table 4).

There was no difference in mean number of bed days, care visits or pleurodesis success rates during study period (table 3). Baseline EQ5D-index was 0.57 (IQR 0.33, 0.74) and ED5D-VAS was 50mm (35, 70) in the IPC group, and 0.58 (IQR 0.33, 0.68) and 50mm (40, 70) in TT group.

There was no statistical difference in EQ5D scores between groups at baseline or at the subsequent monthly visits.

The TT group required 1.3 (SD 1.4) additional TT during the study period, with no additional TT required in the IPC group. The mean drainage during the study period was 17,412ml (SD 17,936) and 2,901ml (SD 2,416) in the IPC and TT group respectively (treatment effect 13,892ml; 95% CI 7669 to 20,116; p<0.001). In the TT group, 17% (6/35) failed their initially randomised treatment, compared to 0/33 in the IPC group. In the TT group 3 (9%) required a chest drain, one of which had talc slurry pleurodesis. Two (6%) patients randomised to TT had an IPC subsequently sited to manage their symptoms. One patient in the TT group (3%) had a medical thoracoscopy, with 3300ml drained at procedure. No patients in the IPC group required a further invasive pleural procedure due to 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 27.0g/L (SD 7.5) and 32.5g/L (SD 5.1) in the IPC and TT cohort respectively (p-value <0.001) (table 3). Subgroup analysis for albumin levels for heart/renal failure patients at 12 weeks was 28.0g/L (SD 6.7) for the IPC group and 33.2g/L (SD 5.3) for TT group. Albumin levels for liver failure patients at 12 weeks were 24.7g/l (SD 9.1) for the IPC group and 29.8g/l (SD 2.9) for TT group (p-value for interaction = 0.83). Seven of the eight patients with HH (88%) received 20% human albumin solution (HAS) at treating physician's discretion.

Adverse events

In total 59% (19/32) of the patients in the IPC arm had at least one adverse event, compared to 37% (13/35) managed with TT (OR 3.13 (1.07, 9.13) p=0.04). In the IPC group there were 12 SAEs. Eight AEs were felt to be secondary to IPC insertion, including leakage from IPC

wound site, significant pain after IPC insertion, IPC malfunction, non-drainage due to pleural septations, and self-resolving localised swelling at IPC insertion site. In one instance the valve fell off the IPC, with resultant fluid leakage**.** The IPC was removed, with another inserted. There was one case of IPC site cellulitis, initially managed with oral antibiotics. This 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, two 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 AEs (all pneumothoraces) secondary to TT. One of these were 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 dyspnoea, 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 non-randomised studies have demonstrated improvements in dyspnoea with IPCs in transudative effusions, with both Srour and Potechin et al reporting an improvement at

two weeks using a baseline and transitional dyspnoea index score in cardiac and renal related effusions, respectively(19, 20) and other observational studies reporting high rates of symptom improvement with IPC in non-malignant effusions(21, 22). 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 breathless 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 terms benefits in breathing, but may ultimately precipitate pleural fluid re-accumulation(23).

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 over 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 studies of patients with primary pleural malignancies(24). This is the first study to demonstrate the extent of the symptom burden in this patient cohort. The choice of intervention in this trial did not affect quality of life scores between treatment groups.

Patients managed with IPCs required fewer invasive pleural procedures, with six patients in the TT cohort requiring 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 breathless 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, or patient preference is unclear. Over half the patients were taking anticoagulants, which may have influenced decisions regarding repeat aspirations.

Indwelling pleural catheters were associated with higher rates of adverse events. Most of these had minimal impact on the patient and the risk of infective complication was low. Risk of IPC-related infection is a commonly cited concern in non-malignant effusions, although pooled analysis of previous rates has shown low rates of 2%(25). Concern about infection is particularly high for patients with end-stage liver disease, who have associated immunosuppression, thrombocytopenia and coagulopathy (26). Specifically for HH, there is concern that infective complications could delay or exclude potential eligible patients from liver transplantation(27). This concern has been amplified by high rates of infection in IPC in series of non-randomised, and predominately retrospective studies of cirrhotic patients, which demonstrate rates between 10 and 25%(28-31). Reassuringly, in our study there was only one case of IPC related infection and none in HH cohort.

An additional concern with use of IPC in transudative effusions, particularly HH, is that repeated large volume drainage may cause nutritional or electrolyte derangement. An earlier study of IPCs in patients with HH demonstrated a small downward trend of serum albumin of 3 g/L, of uncertain clinical significance(29). 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 intravenous human albumin solution (HAS) in this cohort is unestablished. Further research is needed to examine to role of HAS in IPC drainage of HH.

Patient selection may influence treatment response to pleural intervention, with patients whose effusion rapidly and repeatedly reaccumulate 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. 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 conclusion, IPCs did not offer greater control of breathlessness than repeated TT, 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, maintained albumin levels, and should remain the first choice in managing refractory transudative effusions. However, IPCs reduced the number of invasive pleural procedures required with infrequent serious complications, in a population in whom over half were on long-term anticoagulation therapy. IPC may therefore have a role in selected patients who do not tolerate repeated TT, find repeated journeys to hospital difficult or in whom interruption of anticoagulant therapy is undesirable.

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	TT group (n =35)	**IPC group (n 33)**
Age (years) – mean (SD)	73.6 (12.1)	73.2 (12.0)
Female – no. (%)	9 (26)	6 (18)
Primary cause of effusion - no. (%)		
Heart failure	25 (71)	21 (64)
Liver Failure	8 (23)	8 (24)
Renal Failure	2 (6)	4 (12)
Size of effusion – no. (%)		
>1/2 hemithorax	12 (34)	14 (42)
Smoking status – no. (%)		
Never-smoker	13 (37)	16 (48)
Ex-smoker	20 (57)	16 (48)
Current smoker	2 (6)	1 (3)
WHO performance status – no. (%)		
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 - no. (%)		
Right	28 (80)	26 (79)
Previous pleural intervention on same side of effusion in previous 3 months – no. (%)	26 (74)	25 (76)
Duration of symptoms – no (%)		
<1 month	2 (6)	3 (9)
1 to 3 months	5 (14)	6 (18)
3 to 6 months	9 (26)	10 (30)
>6 months	19 (54)	14 (42)
Total volume of pleural fluid drained in previous 3 months (ml) – median (IQR)	1950 (875, 3225)	1790 (1000, 4550)

Total daily furosemide dose (mg) - mean (SD)	52 (60)	62 (76)
Total daily spironolactone dose (mg) - mean (SD)	35 (75)	20 (63)
Receiving anticoagulation - no. (%)	18 (51)	19 (58)
Receiving clopidogrel - no. (%)	3 (9)	2 (6)
Albumin (g/L) – mean (SD)	31.8 (4.8)	31.1 (10.5)
Breathlessness (VAS) – mean (SD)	57 (29)	46 (24)

Table 1: Baseline characteristics by treatment group

	TT group (n=35)		**IPC group (n=31)**		**Treatment effect estimate (95% CI)**	**P-value for interaction**
	Patients with available data	**Result**	**Patients with available data**	**Result**		
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						
<1/2 hemithorax	21/23 (91)	49.1 (24.4)	16/19 (84)	48.9 (31.3)	-0.6 (-17.3, 16.2)	0.67
≥1/2 hemithorax	12/12 (100)	38.0 (28.5)	14/14 (100)	29.1 (24.0)	-6.2 (-26.4, 14.0)	-

Table 2: Outcomes for pre-defined subgroup analysis

	TT group (n=35)		IPC group (n=31)		Treatment effect (IPC vs TT) and 95% CI	P-value
Outcome	**Patients with available data**	**TT group (n=35)**	**Patients with available data**	**IPC group (n=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	NA
Number of intercostal drain (ICD) insertions within 12 weeks of randomisation	35 (100)	0.1 (0.3)	31 (94)	0 (NA)	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/L)	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
NA, Not applicable.						

Table 3: Secondary outcomes

	Number included in analysis		Summary measure			
Outcome	**TT group (n=35)**	**IPC group (n=33)**	**TT group**	**IPC group**	**Treatment effect (IPC vs standard care) and 95% CI**	**P-value**
Breathlessness (VAS)						
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

Table 4: Post hoc analysis of mean monthly breathlessness (VAS)

	TT group (n=35)		**IPC group (n=32)[a]**	
	All	Serious AE	All	Serious AE
At least one adverse event	13	7	19	12
Number of adverse events per patient				
0	22	28	13	20
1	8	5	10	10
2	4	2	5	2
3	0	0	2	0
4	1	0	2	0
At least 1 adverse event deemed to be related to trial interventions (possibly, probably or definitely)	3	2	8	4
Number of adverse events per patient				
0	32	33	24	28
1	3	2	5	4
2	0	0	3	0
At least one adverse event related to the following:				
Pleural infection	0	0	1	1
Chest pain requiring more than oral analgesia	0	0	1	1
Severe bleeding	0	0	0	0
Renal impairment	0	0	0	0
Subcutaneous infection around IPC site	NA	NA	1	0
IPC became blocked	NA	NA	1	0

[a] One IPC patient excluded from this table due to missing data
NA, Not applicable.

Table 5: Adverse events

Figure 1: Consort diagram detailing identification, recruitment, randomization, and follow-up of study participants.

CXR, chest radiograph; IPC, indwelling pleural catheter; TT, therapeutic thoracentesis; VAS, visual analogue scale.

Figure 2 – Change from baseline in daily mean VAS score