The management of recurrent, non-malignant pleural effusions has found itself in a quagmire. While significant advances in the field of malignant pleural diseases have occurred over the years, due to innovation and research efforts, this has not necessarily been the case in the field of non-malignant pleural diseases, except perhaps for pleural infections. Data suggests that despite having a “benign” problem, patients with recurrent, non-malignant pleural diseases may have one-year mortality rates in the range of 25–50% [1]. This, combined with nominally proven treatment options, leaves treating clinicians without confidence in what is truly the best therapeutic option for management.

The historical mantra for the treatment of transudates has generally been to remedy the underlying problem, at which point the pleural disease will subsequently improve [2–4]. While continued optimisation and management of the underlying process should occur, this may not provide adequate palliation from the symptoms and impact arising from recurrent pleural disease.

Since its introduction, the main role of the indwelling pleural catheter (IPC) has been for symptomatic malignant pleural effusion management. However, over the years IPC has been utilised for other, non-malignant disease processes as well, including some common recurrent transudative pleural effusions of cardiac, renal and hepatic origin. Retrospective series of IPC use have promoted advantages such as decreased need for additional pleural procedures and fewer hospital admissions related to exacerbations of the underlying disease process [5–8]. A systematic review and meta-analysis of 350 IPCs placed in 325 patients with benign pleural effusions suggested a subjective improvement in dyspnoea symptoms, with an average rate of spontaneous pleurodesis of 51.3% [9]. In 2017, the Federal Drug Administration from the United States offered clearance for IPCs and use in patients suffering from recurrent transudative effusions, occurring in what appears to be a paucity of convincing data [10].

In this issue of the European Respiratory Journal, WALKER et al. [11] present the first prospective, multicentre, randomised, open-label trial comparing the use of IPC versus intermittent therapeutic thoracentesis (TT) for symptom management of benign effusions. The researchers should be congratulated for the development of a pragmatic trial attempting to answer a question that plagues many of us who manage pleural diseases. For the primary outcome of mean breathlessness score via visual analogue scale (VAS) over 12 weeks, no significant difference was observed between IPC and TT approaches. Analyses of secondary outcomes also revealed a relative equivalence between groups, with no difference in number of hospital days, care visits or pleurodesis outcomes. The authors noted a gradual improvement in the change from baseline daily mean VAS, favouring IPC use, which indeed looks intriguing (figure 2 in [11]). However, they were unable to demonstrate improvement in the IPC group for other metrics, including breathlessness on 1st, 2nd, or 3rd month of enrolment, breathlessness over the first 7 or 28 days.
or quality of life scores. While outcomes of dyspnoea and quality of life appeared relatively equivalent, IPC use appeared worse in the adverse event category; with patients in the IPC branch experiencing significantly more adverse events (59%) compared to the TT group (37%). Even so, the frequency of serious adverse events was similar among groups. Though it occurred minimally in this study, the development of IPC-related pleural infections in patients with hepatic hydrothorax is always worrisome and has been consistently reported more commonly in previous series [12, 13].

Some obvious and unfortunate shortcomings of this trial, underlying statistical issues, are clearly admitted by the authors. First, the final recruitment of the study leaves it underpowered. The authors attribute this to a slower than expected recruitment complicated by the decision of early closure and withdrawal of sponsor funding. Second, they predicted an anticipated difference in VAS scale of 7 mm with a standard deviation of 11 mm, yet their observed standard deviation was closer to 25 mm. This error warrants a larger study which, as noted from the first problem, is likely to be an unreachable target. Third, there were multiple missing VAS scores from a number of enrolled patients. It was elected to utilise a mixed-effects model with a missing-at-random assumption for dealing with this data problem. However, if data is not missing randomly (i.e., sicker patients don’t fill out forms), then the assumptions may be incorrect. The researchers attempted to minimise this potential impact by also performing a sensitivity analysis, which implied that different missing-not-at-random assumptions were only an issue at the extremes (missing data assumed to be very high or low).

So, while these problems are not desired, they are indeed a fact of clinical trials. The authors appear to appropriately acknowledge these limitations, suggesting that the trial adds some prospective data on safety as well as secondary outcomes that remain important to the clinical care of this patient population. They also suggest that a larger trial will probably not have demonstrated a clinically meaningful difference (based on >80% target enrolment and small intergroup VAS breathlessness differences). With all the limitations of such a study, having some data to utilise for decisions is better than none. While this trial does not have the statistical power or completeness to make it a “game changer”, unless another study is done (which seems unlikely), this may be the best we have available for some time.

Thoracentesis use (or non-use) throughout the trial remains thought-provoking. After the initial thoracentesis, approximately half of the TT cohort never underwent another, despite having adequate access, resulting in a relatively low mean rate of 1.3 TT over 12 weeks for the group. This lack of pleural drainage is also likely reflected within the volume of fluid drained as the TT group underwent a mean drainage of 2901 ml, whereas the IPC group underwent a mean drainage of 17 412 ml over the course of the trial. There may be multiple reasons – perhaps patients never needed additional drainage, or they were chosen poorly which resulted in disease processes that didn’t warrant additional interventions. We suspect that these are not likely the answers, as it was evident throughout the trial that there was an overall poor quality of life, ongoing dyspnoea, evidence of persistent pleural disease by imaging and low pleurodesis rates in both groups. However, this begs the question, are we doing anything helpful for these patients?

One advantage of IPC placement in a population such as this may be the ability to avoid additional procedures. In the IPC group, no patients underwent additional drainage procedures after placement. However, IPCs were removed in a few patients for different reasons including one by accident, one due to intolerance while sleeping and one was replaced due to a leaky valve. Within the TT group, six patients underwent additional procedures (3 tube thoracostomy, 2 IPC placement, and 1 thorascopy) under the discretion of treating physicians. It is known that TT is not considered a definitive procedure (like IPC) making interpretation of “failure” and comparison of the two somewhat difficult. The decision to proceed with other interventions was at the discretion of the attending physician and patient as a pragmatic part of the trial, but again without a clear definition of failure. The fact that some clinicians and patients wanted to continue a certain procedure, while others felt it would be better to try something different, makes it hard to argue that IPC offers a clear benefit over TT as there is less “failure”.

In conclusion, the REDUCE trial adds valuable data to the current literature base, but has its limitations and the overall message is that we still need further research in this patient population. Additionally, it appears that this population may have undertreated symptom palliation as demonstrated by poor quality of life and persistent symptoms. The probable multifactorial etiology of these symptoms questions the complete effectiveness of pleural drainage. Perhaps focusing on more specific disease processes (i.e., patients with cardiac failure only) may help to more clearly define whether there is a benefit, what the benefit is, and the best way to obtain it. We also suspect that the most effective way to address such problems is through ongoing multidisciplinary collaboration with subspecialists with respect to both patient care and research efforts.
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References