

Management of malignant pleural effusion

Introduction and background

Malignant pleural effusion is a common clinical problem that may be seen to complicate the management of almost all forms of cancer. There are approximately 300,000 new cases per year across the United Kingdom and United States combined, with more than 40,000 of those cases in the UK alone.[1, 2] General cancer incidence continues to rise, in part due to increasing life expectancy and an older population demographic. In the UK, overall cancer incidence has increased by 7% over the last decade.[3] A similar increase has been evident in the incidence of cases of mesothelioma.[4] These increases in overall cancer incidence lead to a subsequent increase in malignant pleural disease and this represents a trend which is expected to continue.

Advanced metastatic disease in the form of malignant pleural effusion often signifies a limited life expectancy with median survival often quoted as between 3 and 12 months following onset.[1, 5] Treatment priorities are therefore defined by palliative symptom control and in particular, resolution or improvement of dyspnoea.

Several methods are available in the management of malignant pleural effusion including simple pleural aspiration, talc pleurodesis or indwelling pleural catheters (IPCs). Patient selection however remains difficult. The role for each management option, their indications, predictors of success and factors influencing patient selection are all crucial considerations.

Benefit

Patients who undergo intervention for malignant pleural effusion demonstrate statistically and clinically significant improvements in dyspnoea and quality of life. The second therapeutic

intervention in malignant effusion trial (TIME2) demonstrated that 86% of patients with IPCs and 74% of those who underwent drainage and talc pleurodesis experienced clinically significant improvement in their breathlessness. Patients recorded mean improvements of 37mm and 30.2mm respectively at day 42 on a visual analogue scale with an established clinically significant difference of 19mm. Similar improvements were seen in quality of life measurements.[6] The recently published AMPLE study has also confirmed these findings by demonstrating mean improvements of 14.5mm and 17.4mm respectively after only one day.[7] These improvements are consistent even in those patients who exhibit incomplete lung re-expansion or trapped lung suggesting an alternative aetiology to improvement of oxygenation following the resolution of simple compressive atelectasis, despite this factor being evident in the literature.[8, 9] One possible explanation is the resolution of diaphragmatic inversion and abnormal movement. Large effusions are known to cause an increase in intrapleural pressure, leading to flattening or inversion of the hemidiaphragm with subsequent drainage resulting in a return of normal function and position, and thus improvements in dyspnoea.[10, 11]

Treatment options

1) Therapeutic pleural aspiration

A number of treatment options are available, all with the primary objective of palliation of dyspnoea. Convention would suggest that first line management would consist of therapeutic aspiration and this is reflected in the current British Thoracic Society (BTS) Guidelines for the management of malignant pleural effusion.[1] This allows for an assessment of whether the lung is trapped and whether there has been symptomatic improvement; this directs appropriate patient selection prior to proceeding to definitive management. In a few select cases, definitive management may also be provided by systemic chemotherapy. This is possible in some cases of

highly chemosensitive breast cancer, lymphoma and small cell lung cancer, however >90% of effusions recur and require further intervention. Subsequently, there is a lack of consensus with regards to this treatment option due to the high risk of reaccumulation.[12]

Repeated therapeutic pleural aspiration on a symptomatic basis is the recommended treatment choice for frail patients with a poor performance status, or those with a reduced life expectancy of less than one month. However, with the advent of indwelling pleural catheters, which can be placed as a long term solution with little additional morbidity compared with aspiration, this time limit is being questioned. Alternative management options should be considered if life expectancy exceeds one month due to the risk of adhesion formation between the parietal and visceral pleura, and the risks of repeated pleural access. [1] In some instances however, even if prognosis is limited, an indwelling pleural catheter may be considered in these patients, as drainage in the community may provide more appropriate palliation than recurrent day case hospital admissions for therapeutic aspiration.

The optimum volume of fluid to be aspirated remains unclear. The BTS Guidelines recommend less than 1500ml be aspirated at one attempt. Although larger volumes have been documented to have been safely aspirated, including one case recording 6.5 litres in one sitting,[13] recommendations have remained conservative due to perceived increased risks of reexpansion pulmonary oedema and pneumothorax. The presence of cough or chest pain may be the first indication of one of these complications and is often used as an indication to pause or discontinue the procedure.[13-15] In addition, removal of fluid “to dryness” is not a requirement for symptomatic benefit. Large volume aspiration (i.e. around 1000mls), leaving fluid in situ in the pleural space, has been shown to improve dyspnoea in over 80% of patients.[16] This is likely due to the mechanism of dyspnoea in these individuals related to altered breathing mechanics and diaphragm pressure, rather than lung function compromise or lung compression, as discussed above.

2) Intercostal chest drain and talc pleurodesis

Drainage and talc pleurodesis has traditionally been considered the first line, definitive management for malignant pleural effusion and this is reflected in the BTS Guidelines.[1] This can be performed via either talc poudrage at local anaesthetic thoracoscopy or by talc slurry instillation via an intercostal chest drain often performed at the bedside. Numerous other pleurodesis agents are available including bleomycin, tetracycline and iodine along with standard sterile talc. The most commonly used preparation in the UK is talc slurry instillation with documented success rates of 70-80%.[17, 18] This degree of efficacy appears to have been confirmed by the TIME1 trial that recorded pleurodesis failure rates between 20 and 30%.[19]

A recent Cochrane review suggested that talc poudrage may be the most efficacious method of pleurodesis over alternatives such as tetracycline and bleomycin but that superiority over talc slurry or doxycycline is unclear, largely due to significant heterogeneity between studies and the outcomes recorded.[18] The ongoing multicentre, open-label, randomised controlled TAPPS trial (ISRCTN47845793) may help to identify which form of talc administration is more efficacious.[20]

Predicting pleurodesis success remains difficult. The TIME1 randomised control trial demonstrated that small 12Fr Seldinger chest drains failed to meet non-inferiority criteria with regards to pleurodesis success when compared with 24Fr blunt dissection drains. Pleurodesis failure was recorded as 30% versus 24% respectively suggesting that a larger calibre of drain may be required to improve efficacy. The same trial also demonstrated no detrimental effects from non-steroidal anti-inflammatory drugs on pleurodesis efficacy despite long term controversy over their use.[19]

The SIMPLE study (ISRCTN16441661) has been designed to assess whether sonographic features can be used to predict pleurodesis success and reduce the associated inpatient length of stay required. This is based on an observational animal study suggesting that echogenic fibrin strands demonstrated on ultrasound may be associated with higher pleurodesis success.[21, 22] It may also be possible to pre-emptively use ultrasound to predict those patients who are likely to have trapped

lung and who are therefore not suitable for consideration of pleurodesis due to subsequent lack of apposition following drainage.[23]

Aside from failure rates and unsuitability of patients who have poor apposition, there are several well documented disadvantages associated with pleurodesis. Inpatient bed days will be discussed in more detail later, but the mean length of stay associated with talc pleurodesis is 5-7 days.[19] Other documented adverse effects include fever and pain.[18]

3) Indwelling pleural catheters

Indwelling pleural catheters are defined as second line management in the 2010 BTS Guidelines, however over the last decade their use has significantly increased with evidence justifying their place in current practice as an equal first line definitive option, according to patient choice. As previously mentioned, the TIME2 trial demonstrated significant clinical improvements in dyspnoea following the insertion of indwelling pleural catheters without any statistically significant differences when compared to talc pleurodesis. There were also no statistically significant differences with regards to patient reported quality of life.[1, 6]

IPCs offer ambulatory and domiciliary management of malignant pleural effusions allowing greater patient control. Spontaneous pleurodesis related to the catheter, also termed autopleurodesis, has been reported with widely varying frequency of up to 65%.[6, 24, 25] There are also clear benefits in those patients with trapped lung who are not suitable for consideration of pleurodesis as first line management.

A statistically significant increase in the frequency of adverse events has also been documented with IPCs including pleural infection, catheter tract metastases and catheter displacement or blockage. There has however been a documented, statistically significant difference in the number of subsequent pleural procedures required in those patients undergoing IPC insertion, and whilst it is

accepted that this is a positive patient centred outcome, patients still require their pleural space to be accessed on a regular basis and so the clinical significance is less clear.[6, 7]

The frequency with which drainage should be performed from an IPC is unclear, however standard care currently consists of drainage on alternate days. The ASAP trial compared daily drainage with conventional treatment and demonstrated that aggressive management was associated with a statistically significant increase in the rate of autopleurodesis at 12 weeks, rising from 24% to 47% ($p=0.003$). The median time to autopleurodesis was also significantly reduced from 90 days to 54. Adverse events, quality of life and patient satisfaction were not significantly different between the two groups.[24] In addition to these findings, the recently published IPC-PLUS trial has suggested that in patients without evidence of lung entrapment, instillation of talc as a day case procedure demonstrated a statistically significant increase in the rate of pleurodesis when compared with placebo (43% versus 23% $p=0.008$). This would suggest that it may be possible to combine management options by providing patients with an ambulatory, outpatient management opportunity, but also improve the likelihood of pleurodesis to prevent unnecessary ongoing burdensome treatment.[25]

Despite improved autopleurodesis rates in IPC patients with either daily drainage or talc instillation, pleurodesis success still remains inferior when compared to the success documented from talc poudrage, although the two have not been directly compared to date. This may not be an entirely fitting comparison however, as the primary goal of treatment with an IPC is not specifically pleurodesis, but long term management of symptoms. The results of the ASAP and IPC-PLUS trials could be applied to suggest that some value may be derived from the consideration of a combined approach of daily drainage and talc instillation in IPC patients with the hypothesis of a synergistic effect by improving the rate of pleurodesis as well as reducing overall treatment duration, however this requires further investigation.

Health economic impact

The TIME2 trial had found that IPCs reduced the time spent in hospital at the time of the procedure and the number of subsequent pleural procedures required which gave rise to the suggestion that IPCs may offer advantages in terms of cost and the number of inpatient bed days.[6] The authors of the SIMPLE study have estimated costs associated with pleurodesis and the accompanying inpatient stay at £1320 per patient. Based on the estimated number of procedures performed this equates to a cost of approximately £33 million per year to the health service.[21]

Subsequent cost analysis performed on the comprehensive dataset available from the TIME2 showed no significant difference in cost when comparing those treated with IPC and those undergoing drainage and talc pleurodesis. A longer initial hospital stay in the pleurodesis group incurred a higher cost, but significantly higher ongoing costs were associated with regular frequent IPC drainage. Further analysis therefore suggested that in patients with limited survival, IPCs were a less costly alternative. This cost effectiveness is influenced therefore by patient longevity, autopleurodesis rates and the degree of dependence on community nursing input. In a patient population with a median survival of 6 months both treatment options result in similar costs; however if median patient survival is extended to 12 months, talc pleurodesis is superior in the health economic context. [26]

The AMPLE study is a randomised controlled trial that was also designed to investigate the impact of IPC versus pleurodesis on hospitalisation days with the primary end point set as the total number of days spent as an inpatient to either death or to 12 months. This is thought to be a relevant consideration given both the financial impact of inpatient bed days but also the patient centred consideration of patients spending time in hospital when they belong to a cohort who have a very limited median survival. This outcome however only recorded those who remained an inpatient overnight and subsequently did not take into account those undergoing day procedures who still may have spent most of one of their few remaining days in hospital. In this study, IPCs were

associated with a statistically significant reduction in the number of inpatient days. There was a median difference of 2 days between the two groups, however this failed to meet the relatively arbitrary clinically significant difference of 5 days. Most notably, there were a substantial number of inpatient days associated with malignant pleural effusion, regardless of whether patients were treated with IPC or pleurodesis. The median was 10 days and the mean 14.5. There was in fact no statistically significant difference in the number of inpatient days between each group once the admission for the initial management was excluded. This demonstrates the significant requirement for inpatient management in malignant pleural effusion regardless of the management option selected, calling into question the perception of IPCs as providing ambulatory management and offering similar costs to pleurodesis by the reduction in bed days. A specific cost analysis or health economic analysis was not carried out in the AMPLE trial due to the significant worldwide variance in equipment, procedural and inpatient costs.[7]

Future directions

Patient selection for pleurodesis remains difficult. A cohort of patients are not suitable for consideration due to trapped lung resulting in poor apposition. Current methods to identify these patients include chest radiograph appearances following therapeutic aspiration or the use of pleural manometry, however the role of manometry in clinical practice remains the subject of much debate.[27] It has been suggested that several prospective techniques may assist with the identification of these patients, allowing them to proceed directly to a more appropriate intervention, such as IPC, thus avoiding unnecessary procedures. Motion mode (M-mode) ultrasound may allow identification of those with unexpandable lung prior to aspiration by measuring lung movement caused by cardiac pulsation, which in turn is used to define whether the atelectatic lung is free. One small recent retrospective observational study has built on the original findings with regards to the use of M-mode and suggested a sensitivity of 91% and specificity of 88%

in using this technique to detect trapped lung. The appropriate M-mode cut-off value however, has not yet been adequately defined.[23, 28, 29]

The use of ultrasound to predict pleurodesis success in those patients who do exhibit good lung reexpansion with ensuing adequate pleural apposition also remains unclear. An animal study performed in rabbits suggests that sonographic echogenicity may be associated with higher pleurodesis success. Sonographic echogenicity represents a higher complexity or density of fluid which may be reflective of higher protein concentrations. The resultant proposed mechanism for this is that increased activation of fibrin improves efficacy of the pleurodesis agent. The ultrasound finding of echogenicity is non-specific and so the role of ultrasound in predicting pleurodesis success requires further investigation.[1, 21, 22, 30]

One further area requiring ongoing investigation is the management of multiloculated malignant pleural effusion. This cohort of patients present a challenging subgroup as often their effusions cannot adequately be drained using conventional methods to sufficiently palliate symptoms, with residual pleural effusion also preventing attempts at pleurodesis. Local anaesthetic thoracoscopy has been suggested as having a role in disrupting septations prior to either pleurodesis or IPC insertion, however this requires patients to have a good performance status and in those patients with trapped lung, the septations and loculations often recur with the effusion, complicating ongoing management with an IPC. As a result, the role of fibrinolytic therapy has been suggested as having a potential role, particularly given the positive outcomes associated with its use in pleural infection.[31, 32]

Investigation into the use of fibrinolytics in malignant pleural effusion has been ongoing for some time.[33] Recorded outcomes have been variable, but two small randomised controlled trials demonstrated improvements in drainage and lung reexpansion, but no effect on pleurodesis success, and neither study assessed patient centred clinical outcomes.[34, 35] Most recently the randomised controlled TIME3 trial did not demonstrate any statistically significant differences in

patient centred outcomes of dyspnoea or pleurodesis failure, although radiographic appearances improved in keeping with previous studies. Patient enrolment into the trial came from inpatients with a chest drain in situ. As a result, approximately 80% of patients enrolled had a performance status of 3-4. It is therefore possible that results from this relatively frail cohort may not be applicable to the wider population with malignant pleural effusion and that intrapleural fibrinolytics may have a role in certain settings. Further study is also likely required in the IPC population in particular, who may represent a fitter, more ambulatory group and in whom fibrinolytics may have a role.[31]

Conclusions

Malignant pleural effusion is a common pathology that continues to increase in prevalence. It results in significant morbidity and is associated with a limited prognosis. Treatment is therefore palliative in nature but several management options are available. Overall outcomes between traditional pleurodesis and indwelling pleural catheters are similar and decisions should be based on informed patient choice. Various methods are currently under investigation to predict outcomes, improve efficacy and reduce costs but further prospective randomised controlled trials are required.

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