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Outpatient Talc Administration via Indwelling Pleural Catheters for Malignant Effusions.

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Abstract

Purpose of Review:

Malignant pleural effusion is a common cause of breathlessness and signifies advanced disease. Common options for definitive pleural intervention include insertion of an indwelling pleural catheter or talc pleurodesis.

Recent Findings:

Administration of graded talc through an indwelling pleural catheter offers an increased chance of pleurodesis compared to indwelling pleural catheter drainage alone and is not associated with a significant risk of adverse events.

Summary:

In patients where an ambulatory treatment pathway is preferred, the increased chance of pleurodesis with talc administration via indwelling pleural catheter can result in a faster time to device removal and may be associated with better quality of life and symptom scores.

Keywords:

Malignant pleural effusion, pleurodesis, indwelling pleural catheter

Main text

Introduction

Malignant pleural effusions (MPE) are common, affecting up to 15% of all patients with cancer.(1) The majority of patients with MPE are symptomatic, most commonly with breathlessness. The presence of MPE signifies advanced disease with a reduced life expectancy; median survival ranges from 3-12 months.(2) Treatment is therefore aimed at reducing symptoms to optimise quality of life. Many patients with MPE will experience re-accumulation of fluid after initial therapeutic aspiration. Definitive pleural intervention is therefore often preferable to avoid repeat thoracocentesis. (1, 3, 4)

Inducing pleurodesis with a chemical agent to prevent fluid build-up is a well-established and reliable practice, with a recent meta-analysis confirming that graded talc is both efficacious and safe (5) and data consistently suggesting that around 80% of patients will achieve success. (2) However, this approach necessitates inpatient hospital admission, typically of 4-7 days, which may not be preferable when a patient's life expectancy is short.(6)

Indwelling pleural catheters (IPCs) can be inserted as a day case procedure and offer an ambulatory alternative which focuses on symptom control rather than prevention of fluid formation. Evidence shows that patients treated with an IPC spend fewer days in hospital with symptoms controlled as effectively as those receiving a chest drain and talc pleurodesis. (7) Used in isolation, however, IPCs do not confer the same likelihood of achieving pleurodesis as instilling a pleurodesis agent. (5)

2018 saw the publication of the first randomised controlled trial demonstrating that significantly higher success rates of pleurodesis can be achieved by administration of medical talc through the IPC in the outpatient setting. (6) This article provides a summary of that evidence and of other related studies, with consideration of implications on current clinical practice.

Autopleurodesis from an Indwelling Pleural Catheter

Autopleurodesis, in the context of an IPC, may be defined as the spontaneous cessation of pleural drainage without instillation of a chemical agent into the pleural space with

associated with relief of dyspnoea. (8) It is thought that following regular drainage of pleural fluid from the IPC, pleurodesis is achieved by maintaining apposition of the pleura and by the catheter tip or tumour effects generating a low, persistent inflammatory effect. (9)

Published rates of autopleurodesis vary. A post hoc analysis of data collected from 26 patients managed with daily IPC drainage suggested that this may occur in as frequently as 65% of patients (n = 17). (9) A slightly lower overall spontaneous pleurodesis rate of 51% (at 6 weeks post IPC insertion) was noted as a secondary outcome measures from the TIME2 study, which allocated patients to either IPC alone or traditional talc slurry. (7)

However, recent data from adequately-powered, prospective, multicentre studies which measured spontaneous pleurodesis rate as the primary outcome suggest that, in practice, lower autopleurodesis rates are much more likely. For example, in a 12-hospital study in the USA, Wahidi et al randomised 162 patients with an IPC to receive either aggressive (daily) drainage or standard (alternate day) drainage to determine which was superior in achieving autopleurodesis. Autopleurodesis occurred more frequently in the aggressive drainage arm than in the standard arm (47% vs 24% respectively, p = 0.003). The aggressive arm also achieved a faster median time to autopleurodesis (54 days) compared to the standard arm (90 days). (8) The lower spontaneous pleurodesis rate observed in the ASAP trial is likely to reflect the more heterogenous population studied, and thus more closely represent the range of patients seen with MPE in clinical practice, as opposed to the more highly selected patients included in earlier retrospective series.

Further to the above, the AMPLE-2 trial found that 37% of patients receiving daily IPC drainage vs 11% receiving symptom triggered drainage achieved spontaneous pleurodesis at 60 days. Post hoc analysis demonstrated that patients with non-trapped lung were more likely to achieve spontaneous pleurodesis (28% vs 14% with trapped lung). (10) The shorter follow up period and inclusion of patients with trapped lung may explain the lower overall spontaneous pleurodesis rate observed.

Chemical Pleurodesis via IPC

The desire to deliver successful pleurodesis in the ambulatory setting is well recognised, and as such early attempts were made using both temporary drains and IPCs. (11, 12) In 2007, a series of 10 patients demonstrated that chemical pleurodesis agents could be delivered via an IPC. 3/7 patients (43%) receiving Doxycycline instilled through an IPC compared with 2/3 receiving saline placebo achieved pleurodesis. Based on these limited data, the authors concluded that there may be no significant advantage to use of intrapleural Doxycycline after IPC insertion, (13) although more recent evidence has clearly favoured medical talc over other pleurodesis agents. (5)

In a more recent case series medical talc was administered, in a highly protocolised fashion, through the IPCs of 24 patients with MPE at a single UK centre. 22 patients (92%) were discharged home the same day after IPC insertion, with daily drainage of up to 1L and reassessment with ultrasound at 3 days. Talc slurry was administered via the IPC if full lung re-expansion had been achieved and IPC output was <200ml per day. Daily drainage continued after administration of talc, with further ultrasound assessment for absence of

pleural sliding and IPC removal if no fluid had re-accumulated. Successful pleurodesis was achieved in 22 procedures (92%), although with a relatively high rate of complications (21%, n = 5). (14) Although this study demonstrated that talc slurry could be delivered through an IPC safely and effectively in the outpatient setting, its limitations – including being retrospective and utilising a highly-selected patient population – precluded widespread adoption.

In contrast to this, The IPC Plus trial, published in 2018 and carried out in the ambulatory setting, was the first multicentre randomised control trial to robustly test the hypothesis that talc administered through an indwelling pleural catheter is more effective at inducing pleurodesis than the use of an indwelling pleural catheter alone. (6)

154 patients from 18 centres in the UK underwent randomisation. After IPC insertion and maximal fluid drainage they were discharged home the same day. A minimum of 3 further drainages of up to 1L took place before clinical review at day 10, when one further maximal volume fluid drainage was performed. Patients were excluded if a chest x-ray demonstrated <75% pleural apposition or if more than one third of the hemithorax was occupied with fluid. (6)

69 patients received 4g sterile talc in 50ml 0.9% saline through their IPC. 70 patients received 50ml saline placebo. Single blinding was achieved through the use of opaque syringes. Following talc/placebo administration, patients were discharged the same day with subsequent fluid drainage 12-36h later and a minimum of twice-weekly fluid drainages thereafter. Patients were followed up for 70 days after randomisation or until death. (6)

The primary outcome measure of successful pleurodesis at day 35 was achieved in 30/69 (43%) patients who received talc compared to 16/70 (23%) in the placebo group (p = 0.008). Pleurodesis was maintained at 70 days, with 51% (n = 35) of the talc group and 27% (n = 19) of the placebo demonstrating successful pleural apposition (p = 0.003). No significant difference was identified in any secondary outcome, which included effusion size and complexity; number of inpatient days in hospital (4.1 days in talc group and 3 in placebo, p = 0.74); number of adverse events; and mortality. (6)

Of the 21 patients who died during the trial follow up period (7 in the talc group, 14 in placebo), none were attributable to trial interventions. IPC blockage occurred in 6% (5/78) of the talc group and 4% (3/76) of the placebo. (6)

Patients who received talc reported statistically significant better quality of life scores than those who received placebo at all time points and had better symptom scores on a visual analogue scale for chest pain (statistically significant at day 14) and dyspnoea (statistically significant at day 56). (6)

The authors conclude that among patients with sufficiently expanded lung, the outpatient administration of talc through an indwelling pleural catheter for treatment of malignant pleural effusion resulted in a significantly higher chance of pleurodesis at 35 days than an indwelling catheter alone. (6)

<u>Talc Administration via IPC in Practice</u>

Despite the important IPC-Plus result, we have yet to define how best to maximise the benefits of administering talc through an IPC. At this stage, if pleurodesis is the treatment priority, it cannot be inferred that an IPC and talc is a comparable alternative to talc pleurodesis via chest drain or at thoracoscopy, given their relative success rates (43% vs approximately 80%). Rather, IPC-Plus demonstrates that for patients who choose to have an IPC, pleurodesis efficacy can be increased approximately twofold by the appropriate instillation of talc. The comparatively 'low' (43%) rate of success may be attributable to the fact that intermittent IPC drainage does not allow as effective pleural apposition to occur as with traditional chest drainage methods.

In managing MPE, making the choice between an ambulatory IPC and undergoing inpatient talc pleurodesis may be challenging for some, as there are subjective down-sides to each treatment. With the IPC-Plus approach, a higher chance of achieving pleurodesis, and thus removal, may abate some patient concerns regarding the IPC used alone, such as the inconvenience of ongoing drainage. The ASAP study (8) sought to achieve the same effect through daily IPC drainage, and although successful in this aim, it is highly likely that a single instillation of talc would be less burdensome to patients and would also be more economically viable, given the ongoing costs of drainage consumables. Looking ahead, it is likely that treatment protocols combining the benefits of both 'aggressive' drainage and talc instillation will attempt to even further improve pleurodesis success in the ambulatory setting. (15)

It should be noted that no study has yet directly explored the link between earlier pleurodesis and earlier removal of IPC, although these would seem to be logically

associated. In the trial setting, particularly in IPC-Plus, physician attitude to the then novel intervention is likely to have had a strong influence, with rates of IPC removal due to cessation of fluid drainage showing no difference between the treatment arms. This may have been due to uncertainty regarding the likelihood of fluid re-accumulation and thus the optimal timing for IPC removal; many sites elected to 'wait and see,' leaving an IPC in situ for a number of weeks post-pleurodesis, before arranging removal. With this in mind, future research into optimal timing for IPC removal after talc administration may be informative.

IPC-Plus showed encouraging signals with regards to subjective quality of life and symptom measures. The talc group consistently had more favourable scores at trial follow-up visits, with post-hoc analysis confirming that this effect was statistically significant for quality of life and chest pain when aggregated across the whole follow-up period. However, these findings must be interpreted with caution as their clinical relevance is less certain as, aside from dyspnoea measured on a visual analogue scale, (16) there is very little robust data describing the minimally important difference for symptoms in pleural disease.

There are other important limitations to the IPC-Plus results. Firstly, the short primary endpoint and follow-up duration means that comments on the long-term efficacy of talc delivered via IPC cannot be commented upon. In addition, it is also possible that the UK patient population, with a relatively high incidence of malignant mesothelioma, is less representative of that in other nations.

In general, however, the results of the IPC-Plus trial represent an important advance over previous recommendations for the management of MPE. By highlighting how an IPC can be

used in a more versatile fashion, practitioners are now able to have a more honest and realistic discussion with their patients regarding the best management approach for that individual. The study also showed that even those with a minor degree of unexpanded lung – a group previously thought unlikely to benefit from attempts at pleurodesis – can be treated successfully.

Conclusion

Symptomatic MPE remains an important and commonly encountered issue for both patients and health care professionals. Management strategies should focus on optimising quality of life and patient preferences should inform treatment decisions. For those patients in whom ambulatory management is preferred, talc administration via IPC offers an increased chance of pleurodesis and does not appear to be associated with a significant risk of adverse events. Future research, including health economic and longer-term clinical studies, will hopefully allow both clarification of the wider benefits of this approach and the potential for further improving pleurodesis outcomes.

Key Points

- Management of symptomatic malignant pleural effusion should be guided by patient choice
- Outpatient talc administration via indwelling pleural catheter increases the rate of pleurodesis in comparison to IPC drainage alone
- No significant increase in adverse events has been seen in patients undergoing talc pleurodesis via IPC

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Conflicts of Interest

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