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Interventions for the management of malignant pleural effusions: an updated network meta-analysis

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To the Editor:

Malignant pleural effusion (MPE) is a commonly encountered clinical problem, causing disabling breathlessness and affecting up to 15% of all patients with cancer [1]. Wider availability of indwelling pleural catheters (IPCs) and recent development of different IPC drainage strategies has expanded the range of treatment approaches. Incorporating results from several high quality, large randomised controlled trials (RCTs), we have updated the 2016 *Cochrane* review [2] to determine the efficacy of different interventions for MPE. We performed a multiple interventions systematic review, pairwise meta-analyses and network meta-analyses (NMA) with the primary outcome of pleurodesis success. Secondary outcomes included adverse events, breathlessness, quality of life, cost, mortality, survival, duration of inpatient stay and patient acceptability [3]. Here, we summarise key findings of the review to increase accessibility of the "take home" messages among the wider respiratory community.

Full details of the methods are reported in the *Cochrane* publication [3]. Through database searches, review of references of relevant publications and trials registry screening, we identified RCTs of intrapleural interventions for adults with symptomatic MPE. Two reviewers independently extracted data from eligible RCTs and completed the Cochrane risk of bias assessment. Where two or more studies provided direct evidence on a treatment comparison, we performed pairwise meta-analysis using a random-effects model. For studies deemed to be jointly randomisable (whereby it is assumed that patients who fulfil inclusion criteria are equally likely to be randomised to any of the interventions), we performed a multiple interventions NMA of primary outcome data and secondary outcomes with sufficient data using a Bayesian random-effects model.

NMA of interventions in a connected network provided odds ratio estimates representing all possible pairwise comparisons, including those that had not been directly compared in RCTs. Estimates of the rank of each intervention in the network, with a 95% credible interval (Cr-I) were generated. We performed sensitivity analyses for our primary outcome by excluding trials with certain characteristics, such as those at high risk of bias, to assess whether heterogeneity was reduced. We assessed the certainty of evidence using GRADE and presented summary of findings tables for the most commonly studied interventions.

1415 records were identified, from which 156 full texts were assessed for eligibility. 18 studies met inclusion criteria, providing data from 2079 additional participants. These were combined with the 62 studies included in the 2016 review, giving a total of 80 studies of 5507 participants.

The primary NMA on pleurodesis failure included 55 studies (3758 participants) of 21 interventions, with five additional interventions included since the last iteration of this review. A number of interventions were not felt to be jointly randomisable (such as specific surgical techniques or tumour dependent intra-pleural chemotherapy) and hence not included in the network. Talc slurry was the most studied agent (907 participants randomised across 19 studies) and therefore used as the comparator in our summary of findings (table 1).

Our primary NMA evaluating pleurodesis failure provided weak evidence that talc poudrage may have fewer pleurodesis failures than talc slurry *via* a standard chest drain (OR 0.50 (95% Cr-I 0.21–1.02)). However, pairwise meta-analysis of four statistically homogenous trials indicated comparable pleurodesis efficacy (OR 0.81 (95% CI 0.61–1.08)), further supported by a sensitivity NMA restricted to studies at low

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Talc slurry and poudrage are effective pleurodesis agents. IPCs have lower pleurodesis rates but comparable breathlessness control and reduced risk of repeat invasive procedures. It is essential that patients have access to a range of treatment strategies. https://bit.ly/38v30yw

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TABLE 1 Summary of findings for pleurodesis failure[#]

	Relative effect, network estimate	Relative effect[¶]	Anticipated absolute effect[+]			Interpretation of findings[§]
			With talc slurry	With intervention	Difference	
Talc slurry	Reference comparator	Reference comparator	18 failures per 100 participants (11–24)	Not estimable	Not estimable	Reference comparator
Talc poudrage	0.50 (0.21–1.02)	0.78 (0.16–2.08)	18 failures per 100 participants (11–24)	10 failures per 100 participants (4–19)	−8 (−15–0), *i.e.* 8 fewer failures per 100 participants	Probably comparable
Bleomycin	2.24 (1.10–4.68)	3.93 (1.10–16.94)	18 failures per 100 participants (11–24)	32 failures per 100 participants (17–52)	15 (2–32), *i.e.* 15 more failures per 100 participants	May be inferior
IPC: not daily drainage	7.60 (2.96–20.47)	8.60 (2.26–30.15)	18 failures per 100 participants (11–24)	62 failures per 100 participants (36–82)	44 (20–63), *i.e.* 44 more failures per 100 participants	Probably inferior
Doxycycline	2.51 (0.81–8.40)	1.89 (0.32–8.84)	18 failures per 100 participants (11–24)	35 failures per 100 participants (13–65)	17 (−3–46), *i.e.* 17 more failures per 100 participants	May be inferior
Placebo	15.90 (3.76–79.90)	17.46 (3.33–97.26)	18 failures per 100 participants (11–24)	77 failures per 100 participants (42–95)	59 (26–77), *i.e.* 59 more failures per 100 participants	Probably inferior

Data are presented as odds ratio (95% credible interval). IPC: indwelling pleural catheter. [#]: total studies in network meta-analysis (NMA): n=55, total participants in NMA: n=3758, interventions in NMA: n=21; [¶]: network estimate from sensitivity analysis of studies at low risk of bias, according to the Cochrane risk of bias assessment criteria, these data are included within the summary of findings to reflect the ORs and credible intervals from the network estimates in which we have the greatest level of certainty in the evidence; [+]: calculated using data from primary outcome network of pleurodesis failure; [§]: based on GRADE outcome of certainty in the evidence.

risk of bias (OR 0.78 (95% Cr-I 0.16–2.08)). IPCs without daily drainage were less likely to effect a definitive pleurodesis (enabling IPC removal) than talc slurry (OR for pleurodesis failure 7.60 (95% Cr-I 2.96–20.47)); however, pleurodesis efficacy may be increased by daily IPC drainage or administration of talc slurry *via* the IPC.

There was insufficient comparable data to perform a NMA on post-intervention breathlessness outcomes; however, additional data from newer RCTs did enable pairwise meta-analysis of post-intervention 100 mm visual analogue dyspnoea scores. Data from two studies demonstrated that IPCs (without daily drainage) provide equivalent breathlessness control when compared to talc slurry (mean difference −6.12 mm (95% CI −16.32–4.08)).

Meta-analysis of data from three studies demonstrated that participants who received an IPC were less likely to require a repeat invasive pleural procedure than those treated with talc slurry (OR 0.25 (95% CI 0.13–0.48)). The risk of repeat invasive intervention when treated with talc poudrage was similar to talc slurry (OR 0.96 (95% CI 0.59–1.56)).

We used NMA to compare rates of procedure-related fever and pain, which were the most widely reported adverse events. There was no statistical evidence for differences between commonly used interventions. Full results are available in the *Cochrane* publication [3].

Our updated review is the largest systematic review and NMA to date of evidence for the management of MPE, which attempts to combine all available randomised data on the wide variety of interventions. We included six additional studies evaluating IPCs which, when combined with the two studies included in the previous review, establish that IPCs provide an alternative first-line approach to MPE management. Although associated with lower definitive pleurodesis rates, comparable breathlessness control can be achieved, with a lower risk of requiring a repeat invasive pleural procedure compared to talc slurry. This may be advantageous to individuals who wish to avoid an inpatient stay and to minimise future invasive procedures. None of the included studies have quantified the overall healthcare utilisation of IPCs, including community drainages, which is a consideration for future research.

We now highlight that since comparable breathlessness control can be achieved by commonly utilised interventions, patient choice is likely to be a key determinant when selecting an intervention. This emphasises the importance of informed discussion to facilitate joint decision making.

The diversity of outcome measurement scales used by studies which assessed patient-related quality of life and symptom control precluded NMA of these outcomes. Although secondary outcomes of our review, these are important considerations when selecting a management strategy. The development of MPE specific, validated patient-reported outcome measurement tools would be hugely beneficial when combining data from future RCTs to increase the applicability of evidence to everyday practice.

The risk of bias in the included RCTs was substantial; only three out of 80 were judged as low risk across all seven domains of the Cochrane risk of bias tool. We added summary of findings tables to this updated article and chose to include results from our sensitivity analysis of studies at low risk of bias (which we defined as a maximum of one high-risk domain), to reflect the estimates in which we had the greatest level of certainty. This produced a reduced heterogeneity estimate, indicating that bias may have contributed to the heterogeneity observed in the primary NMA. Methodological differences between studies, including definition of pleurodesis failure and time-point at which this was assessed, in addition to variation in drug doses and effects of differing tumour subtypes, may also have contributed to the heterogeneity observed, signifying the complexity of the MPE condition and its treatments.

Based on the available evidence, talc slurry and talc poudrage are effective methods for achieving a pleurodesis. Whilst IPCs are less likely to effect a pleurodesis, they confer a lower risk of requiring repeat invasive intervention. Breathlessness control is comparable for these commonly utilised interventions. It is therefore essential that a range of treatment strategies are accessible to patients depending on their clinical situation and that personal preferences are considered.

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