Online Appendix D4 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D4 Evidence Review and Protocol

D4 For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?

Contents

Question Evidence Review

D4 For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?

Background

Chest drain insertion with talc pleurodesis and indwelling pleural catheters (IPCs) provide definitive treatment options in the management of malignant pleural effusion (MPE). Talc pleurodesis has long been considered the standard of care, however, understanding the role of IPCs in comparison is key to provide optimal options to patients with MPE.

Outcomes

Quality of life, length of hospital stay, need for re-intervention, symptoms (breathlessness, chest pain), complications and pleurodesis rates

Evidence Review

The initial literature search identified 47 papers of which eight were deemed relevant. This included four randomised controlled trials[1-4], two prospective cohort studies[5,6] and two retrospective cohort studies[7,8].

Quality of Life

Four studies reported quality of life measures for indwelling pleural catheter versus talc slurry pleurodesis but meta-analysis was not possible due to heterogeneity in the time points and methods used to measure quality of life measure. A summary of the results is shown in Table D4a.

Although two studies used the quality of life visual analogue score (VAS), these were reported as mean VAS by Thomas et al[1] and as the proportion of patients achieving a minimally important difference (defined as one half of standard deviation at baseline) by Fysh et al. A prospective comparator study of IPC vs talc slurry pleurodesis suggested a higher proportion of patients achieved >1 minimally important improvement in quality of life VAS with IPC compared to talc slurry pleurodesis (93% vs 50%, $p = 0.002$), but this only included 15 and 12 patients respectively and was a secondary outcome in a non-randomised study.[5]

Length of Stay

Five studies reported on length of hospital stay[1-3,6,7] (Table D4b) and four studies reported on total number of inpatient days from intervention to death or completion of follow-up[1,3,5,8] (Table D4c). Only one study reported mean hospital stay data[7], with the remainder reporting median hospital stay. Overall, patients managed by IPC spent less time in hospital for both the initial procedure and total inpatient days to those managed with talc slurry pleurodesis.

Need for re-intervention

Four studies reported on pleural intervention[1-3,8], but one study was excluded from the meta-analysis because re-intervention was recorded on a per-patient basis[8]. Meta-analysis of the remaining three studies demonstrated that pleural re-intervention was higher with talc slurry (251 per 1000 patients) than IPC (78 per 1000 (43 to 138)) (Figure D4a).

Symptoms (breathlessness, chest pain)

Six studies reported on symptoms, but meta-analysis was not possible because of heterogeneity in the methods chosen to measure dyspnoea.[1-6] Although three studies used VAS[1,2,5], two did not provide raw numbers[1,2]. All studies demonstrated significant improvements in dyspnoea following either IPC insertion or talc pleurodesis, but all studies reporting dyspnoea showed no significant difference between the two groups. Data are summarised in Table D4d.

Figure D4a: Need for re-intervention (IPC versus talc slurry)

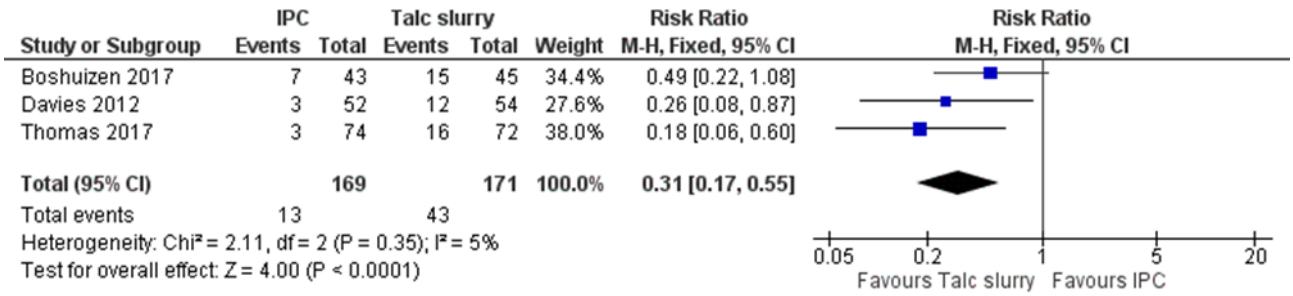


Table D4a: Comparison of quality of life for patients with malignant pleural effusion treated with an indwelling pleural catheter or talc slurry pleurodesis

Study	Time	QoL tool	IPC	TPS	Difference	*p*
			Mean (mean difference) [95% CI]			
Davies 2012[2]	6 weeks	EORTC-QLQ30	59.0 [51.8, 66.3]	48.3 [50.1, 56.6]	4.8 [-1.6, 11.2]	0.14
	3 months	"		Data not reported		NS
	6 months	"		Data not reported		NS
Thomas 2017[1]	2 days	VAS	60.3 [50.9, 69.7]	58.5 [48.9, 68.1]	-1.8 [-10.6, 7.1]	0.74
	30 days	"	61.5 [52.2, 70.8]	67.3 [57.6, 77.0]	5.8 [-3.1, 14.7]	0.17
	6 months	"	67.4 [57.6, 77.3]	66.1 [55.5, 76.7]	-1.3 [-11.6, 9.1]	0.89
	1 year	"	61.7 [50.9, 72.4]	56.3 [45.0, 67.6]	-5.3 [-17.3, 6.6]	0.43
Thomas 2017[1]	8 days	EQ5D	34.1 [29.5, 38.7]	35.3 [30.6, 40.0]	1.2 [-2.7, 5.1]	0.48
	30 days	"	35.2 [30.6, 39.8]	34.5 [29.8, 39.2]	-0.7 [-4.6, 3.2]	0.86
	6 months	"	33.9 [29.1, 38.7]	33.1 [28.0, 38.1]	-0.8 [-5.3, 3.7]	0.84
	1 year	"	32.4 [27.3, 37.5]	31.5 [26.2, 36.8]	-0.9 [-6.1, 4.2]	0.83
			Mean score change per day [95% CI]			
Walker 2016[6]	6 weeks	FACIT-PAL	0.16 [-0.04, 0.35]	0.32 [0.09, 0.54]	-	>0.05
	6 weeks	LCADLS	-0.07 [-0.15, 0.01]	-0.14 [-0.32, 0.04]	-	>0.05
	6 weeks	FACIT-TS		Data not reported		>0.05
			Rate of significant QoL improvement (no. patients)			
Fysh 2012[5]	7 days	VAS	93% (14/15)	50% (6/12)	-	0.02

EORTC-QLQ30 – European Organisation for Research and Treatment of Cancer QOL Core Questionnaire 30; EQ5D – EuroQol-5D; FACIT-PAL - Functional Assessment of Chronic Illness Therapy – Palliative Care; FACIT-TS – Functional Assessment of Chronic Illness Therapy – Treatment Satisfaction; IPC – intrapleural catheter; LCADLS – London Chest Activity of Daily Living Scale; NS – not significant; QoL – quality of life; TPS – talc slurry pleurodesis; VAS – Visual Analogue Score

Table D4b: Summary of trials reporting length of hospital stay in patients treated with IPC versus talc slurry pleurodesis

Study	Design	Study size	IPC	TPS	*p*
			(median days [IQR])		
Davies 2012[2]	RCT	106	0 [0-1]	4 [2-6]	<0.001
Boshuizen 2017[3]	RCT	94	0	5	0.0001
Thomas 2017[1]	RCT	146	1 [1-2]	3 [3-4]	0.001
Walker 2016[6]	PCS	66	2 (range 0-20)	10 (range 5-58)	-
			(mean ± SD days)		
Putnam 2000[7]	RCA	168	8.85 ± 8.89	8.36 ± 5.52	-

IQR – interquartile range; PCS – prosective comparative study; RCA – retrospective cohort analysis; RCT – randomised controlled trial

Table D4c: Summary of trials reporting total number of inpatient days in patients treated with IPC versus talc slurry pleurodesis

Study	Design	Study size	Follow-up	IPC	TPS	*p*
				median (days [IQR])		
Boshuizen 2017[3]	RCT	94	6 months	2	7	0.0016
Thomas 2017[1]	RCT	146	12 months	10 [3-17]	12 [7-21]	0.03
Fysh 2012[5]	PCS	75	12 months	6.5 [3.75-13]	18 [8-26]	0.02
Ost 2018[8]	RCA	2275	Until death	23 [12-51.5]	34 [18-68]	-

IQR – interquartile range; PCS – prosective comparative study; RCA – retrospective cohort analysis; RCT – randomised controlled trial

Complications

Four studies reported on complications/adverse events and were included in the meta-analysis. One further retrospective cohort study was excluded as results were presented as absolute number of adverse events rather than per-patient. Meta-analysis showed that there were fewer patients who experienced complications in the talc slurry group (204 per 1000) compared to the IPC group (279 per 1000 (198 to 396)) (Figure D4b).

Figure D4b: Complications (IPC versus talc slurry)

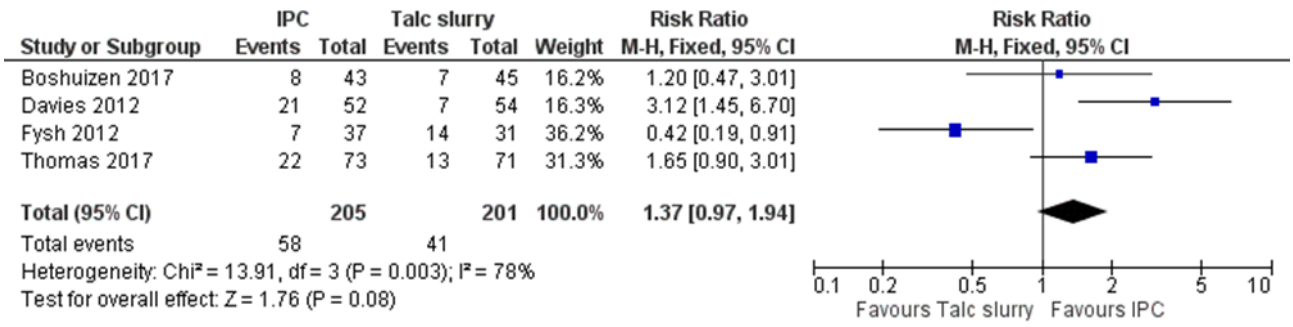


Table D4d: Summary of trials reporting dyspnoea scores for patients with malignant pleural effusion treated with an indwelling pleural catheter or talc slurry pleurodesis

Study	Time	QoL tool	IPC	TPS	Difference	*p*
			Mean (mean difference) [95% CI]			
Davies 2012[2]	6 weeks	VAS	24.7 [19.3, 30.1]	24.4 [19.4, 29.4]	0.2 [-6.8, 7.1]	0.96
	3 months	"	Data not reported		-8.9 [1.7, 19.4]	0.10
	6 months	"	Data not reported		-14.0 [-25.2, -2.8]	0.01
Thomas 2017[1]	1 days	VAS	64.5 [51.4, 75.5]	69.7 [56.5, 82.9]	5.2 [-3.2, 13.7]	0.22
	30 days	"	69.7 [56.7, 82.6]	72.2 [59.0, 85.2]	2.6 [-5.9, 11.1]	0.55
	6 months	"	71.1 [57.8, 84.5]	71.2 [57.3, 85.1]	0.0 [-9.9, 10.0]	0.99
	1 year	"	69.4 [55.4, 83.4]	59.0 [44.6, 73.4]	-10.4 [-21.9, 1.1]	0.07
			% patients with improvement in QoL (no. patients)			
Fysh 2012[5]	7 days	VAS	93% (14/15)	79% (11/14)	-	0.33
			AUC			
Boshuizen 2017[3]	2 weeks	MBS	1.8	1.8	-	0.95
	2 weeks	"	3.3	3.6	-	0.70
			*Assumed median**			
Demmy 2012[4]	30 days	DI	8.5	6.1	-	0.047
Walker 2016[6]	6 weeks	FACIT-PAL	Data not reported			>0.05

* Data format not stated, but similar data reported as median

DI – Dyspnea Index; FACIT-PAL – Functional Assessment of Chronic Illness Therapy – Palliative Care; IPC – intrapleural catheter; MBS – modified Borg scale; QoL – quality of life; TPS – talc pleurodesis; VAS – Visual Analogue Score

Pleurodesis rates

Pleurodesis is a challenging endpoint to review and has a number of similarities with the re-intervention analysis. The definition of pleurodesis was variable across the studies identified and could be radiologically-defined or clinically-defined, which were not likely to describe the same outcome. Accordingly, it was not possible to undertake a meta-analysis.

One randomised trial[4] of IPC vs talc slurry pleurodesis reported a specific pleurodesis outcome rather than re-intervention rate, but did not provide the definition of pleurodesis. The study reported a pleurodesis success rate of 86% in the talc slurry pleurodesis group and 68% in the IPC group ($p = 0.19$).

Evidence statements

Talc slurry pleurodesis and indwelling pleural catheters appear to improve dyspnoea and quality of life scores, but there are no differences between the two treatments (**Ungraded**)

IPC insertion appears to be is associated with a shorter length of initial hospital stay at the time of intervention and fewer subsequent inpatient days (**Ungraded**)

Indwelling pleural catheters appear to be associated with a reduced need for further pleural intervention (defined as requirement for a further pleural breaching procedure) when compared with talc slurry pleurodesis (**Moderate**)

There appears to be no difference in the number of adverse events experienced by patients treated with talc slurry pleurodesis or IPC (**Very Low**)

Recommendation

- Patients without known non-expandable lung (for a definition of non-expandable lung please see Supplementary Online Appendix D7) should be offered a choice of indwelling pleural catheter (IPC) or pleurodesis as first line intervention in the management of malignant pleural effusion. The relative risks and benefits should be discussed with patients to individualise treatment choice (**Conditional**)

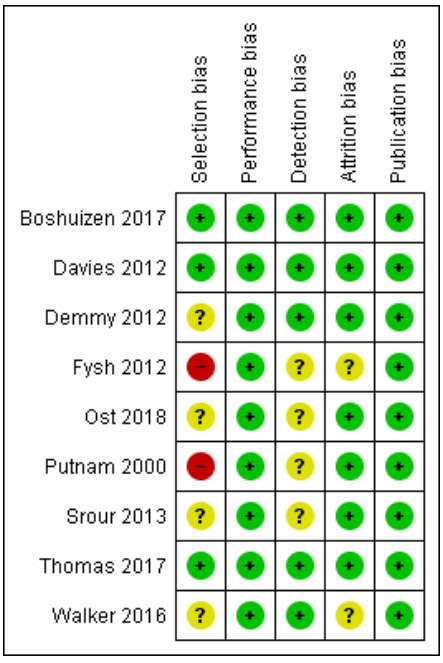
Good Practice Points

- ✓ The psychological implications and potential altered body image aspects of having a semi-permanent tube drain in situ should not be underestimated and must be considered prior to insertion
- ✓ All patients who have had an IPC inserted should be referred to the community nursing team on discharge for an early assessment of the wound site, symptom control, support with IPC drainage and removal of sutures.
- ✓ Patients and their relatives should be supported to perform community drainage and complete a drainage diary if they feel able to do so, to promote independence and self-management
- ✓ Complications such as infection refractory to community management, suspected drain fracture, loculations or blockage with persistent breathlessness should be referred back to the primary pleural team for further assessment

Research Recommendation

- Further research is needed on patient and carer experience with indwelling pleural catheters (IPCs)

Risk of bias summary



GRADE analyses

For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?

Population: Adults (18+) with malignant pleural effusion
Intervention: Indwelling pleural catheter (IPC)
Comparator: Talc slurry pleurodesis

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Pleurodesis	IPC	
Re-intervention	340 (3 studies)	RR 0.31 (0.17 to 0.55)	**251 per 1000**	**78 per 1000** (43 to 138)	⨁⨁⨁◯ **MODERATE** [a]
Complications	406 (4 studies)	RR 1.37 (0.97 to 1.94)	**204 per 1000**	**279 per 1000** (198 to 396)	⨁◯◯◯ **VERY LOW** [a,b]

CI: Confidence interval

Explanations

a. Some imprecision, CIs cross one MID
b. High degree of inconsistency across the studies

Recommendation Table

Question Details

POPULATION:	Adults aged 18+ with malignant pleural effusion
INTERVENTION:	Indwelling pleural catheter (IPC)
COMPARISON:	Talc slurry pleurodesis
OUTCOMES:	Quality of life; length of hospital stay; need for re-intervention; symptoms (breathlessness, chest pain); complications; pleurodesis rates

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
☐	☐	☐	☒	☐

CONCLUSIONS

Recommendation

Patients without known non-expandable lung should be offered a choice of indwelling pleural catheter (IPC) or pleurodesis as first line intervention in the management of malignant pleural effusion

Justification

Talc slurry pleurodesis and indwelling pleural catheters appear to improve dyspnoea and quality of life scores, but there are no differences between the two treatments (**Ungraded**)

IPC insertion appears to be is associated with a shorter length of initial hospital stay at the time of intervention and fewer subsequent inpatient days (**Ungraded**)

Indwelling pleural catheters appear to be associated with a reduced need for further pleural intervention (defined as requirement for a further pleural breaching procedure) when compared with talc slurry pleurodesis (**Moderate**)

There appears to be no difference in the number of adverse events experienced by patients treated with talc slurry pleurodesis or IPC (**Very Low**)

Subgroup considerations

There was not enough evidence for subgroup consideration (trapped lung, non-trapped lung, unknown)

Research priorities

Further research is needed on patient and carer experience with indwelling pleural catheters (IPCs)

References

1. Thomas R, Fysh ETH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomized clinical trial. *JAMA.* 2017;318(19):1903-1912.
2. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA.* 2012;307(22):2383-2389.
3. Boshuizen RC, Vd Noort V, Burgers JA, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). *Lung Cancer.* 2017;108:9-14.
4. Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). *Journal of the National Comprehensive Cancer Network.* 2012;10(8):975-982.
5. Fysh ETH, Waterer GW, Kendall PA, et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. *Chest.* 2012;142(2):394-400.
6. Walker S, Zubrinic M, Massey C, Shargall Y, Bedard E, Darling G. A prospective study of patient-centred outcomes in the management of malignant pleural effusions. *Int J Palliat Nurs.* 2016;22(7):351-358.
7. Putnam JB, Jr.;, Walsh GL, Swisher SG, et al. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. *Ann Thorac Surg.* 2000;69(2):369-375.
8. Ost DE, Niu J, Zhao H, Grosu HB, Giordano SH. Quality gaps and comparative effectiveness of management strategies for recurrent malignant pleural effusions. *Chest.* 2018;153(2):438-452.

Question Protocol

Field	Content
Review Question	For adults with malignant pleural effusion, is an indwelling pleural catheter better than talc slurry pleurodesis at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	One of a series of questions comparing the standard of care (chest tube and talc slurry) with another intervention. Is an indwelling catheter superior to talc slurry?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion
Eligibility criteria – intervention(s)	Indwelling pleural catheter (IPC)
Eligibility criteria – comparators(s)	Talc slurry pleurodesis
Outcomes and prioritisation	Quality of life Length of hospital stay Need for re-intervention Symptoms (breathlessness, chest pain) Complications Pleurodesis rates
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis

Proposed sensitivity / subgroup analysis, or meta-regression	Trapped lung Non-trapped lung Unknown
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 — Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler — Quality of evidence assessment Gradepro — Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Talc slurry through an intercostal tube remains the standard of care. What is the evidence that informs this practice?