Online Appendix D8 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D8 Evidence Review and Protocol

D8 For adults with malignant pleural effusion and septated effusion (on radiology), are intrapleural enzymes better than surgery, or no treatment at improving clinical outcomes?

Contents

Question Evidence Review

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Background

Patients with malignant pleural effusion (MPE) and septated effusion are less likely to benefit from pleural fluid drainage because percutaneous drainage alone cannot effectively drain the effusion. This group of patients has been reported as having a worse prognosis than other patients with MPE.[1] Septated effusions can occur both in inpatients with chest drains and ambulant patients with indwelling pleural catheters (IPC). Effective drainage of the pleural space, either by decortication or by intrapleural enzymes, may improve symptoms. However, surgical intervention is invasive, and carries a significant risk of morbidity and mortality, and may not be appropriate in these patients. This review assesses the evidence for intrapleural agents to achieve clearance of septated malignant effusion versus surgical intervention and versus placebo.

Outcomes

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

Evidence Review

1. Intrapleural enzymes versus surgery

No studies were identified through the literature search that were relevant to the question. Furthermore, no studies were identified that looked at the role of surgery in patients with septated MPE. One reason for this may be because this is best identified on ultrasound and surgeons have not historically performed ultrasound in their patients. The lack of literature supports the view that surgery is rarely used for these patients.

2. Intrapleural enzymes versus no treatment

Four relevant studies were identified in the literature search. Two randomised controlled trials (RCTs) directly related to the question, with one using failure of complete drainage as a surrogate for septations on radiology[1] and the other using loculations on computed tomography (CT)[2]. In a further RCT, unselected MPE patients were enrolled rather than specifically recruiting patients with septated effusion.[3] All RCTs recruited inpatients with chest drains. In contrast, a retrospective case series addressed patients with IPC and a variant of different fibrinolytics (tissue-plasminogen activator, urokinase and streptokinase).[4]

Quality of life

Only one study looked at quality of life as a secondary outcome and reported no difference between the intervention group (intrapleural enzymes) and the placebo group (no treatment) in inpatients with chest drains.[1]

Length of hospital stay

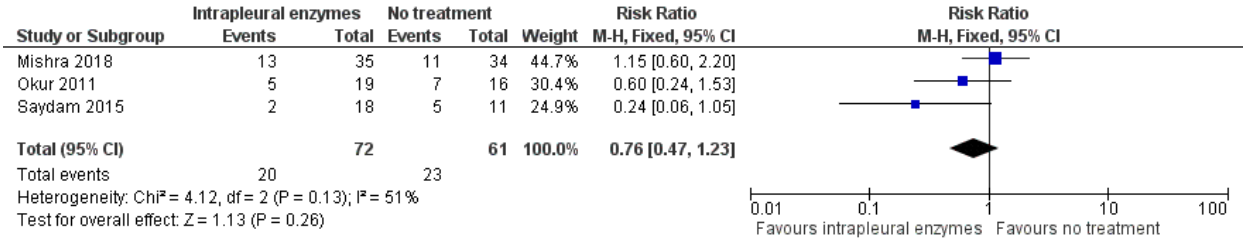
Length of hospital stay was reported as a secondary outcome in the Mishra et al study and reported significantly shorter hospital stay in inpatients treated with intrapleural enzymes versus the no treatment group (6.2 ± 2.7 days versus 8.7 ± 6.5 days respectively, mean ± SD, $p = 0.049$).[1]

Need for re-intervention and pleurodesis rates

The need for re-intervention and pleurodesis rates were reported in all trials, but different definitions were used. In the inpatient trials, Mishra at al defined this as need for a further pleural intervention or symptomatic recurrence, with radiographic evidence of recurrence, within one year.[1] Okur et al defined it as recurrent effusion occupying >50% of the hemithorax or need for a further pleural intervention within three months[3] and Saydam et al defined it as need for a further drainage within 30 days[2]. Overall, the

meta-analysis of the RCTs showed that that pleurodesis failure rate was lower in the intrapleural enzyme treated group (287 per 1000 (177 to 464)) when compared to the no treatment group (377 per 1000) (Figure D8a).

Figure D8a: Need for re-intervention and pleurodesis rates (intrapleural enzymes versus no treatment)



Symptoms (breathlessness, chest pain)

Breathlessness was reported by Mishra et al, based on visual analogue scale diary[1], and by Saydam et al. as the need for oxygen[2]. Chest pain was not reported in any trials. Both studies were included in a meta-analysis and showed a decrease in breathlessness in the intrapleural enzyme group (278 per 1000 (168 to 470)) when compared to the no treatment group (480 per 1000) (Figure D8b).[1,2]

Figure D8b: Symptoms (breathlessness, chest pain) (intrapleural enzymes versus no treatment)

Complications

No studies reported on complications, or adverse events, when treating MPE patients with intrapleural enzymes.

Evidence Statements

There is insufficient evidence to determine if intrapleural enzymes are better than surgery at improving clinical outcomes in adults with malignant pleural effusion and septated effusion (on radiology).

For inpatients with a chest drain:

Intrapleural fibrinolytic treatment may shorten hospital stay in patients with malignant pleural effusion and septated effusion when compared to no treatment (**Ungraded**)

Intrapleural fibrinolytic treatment appears to decrease pleurodesis failure rate, when compared to no treatment, in patients with malignant pleural effusion and septated effusion (**Very Low**)

Intrapleural fibrinolytic treatment appears to decrease breathlessness, when compared to no treatment, in patients with malignant pleural effusion and septated effusion (**Very Low**)

For ambulant patients with indwelling pleural catheters:

Intrapleural fibrinolytics, when compared to no treatment, may improve breathlessness in patients with malignant pleural effusion and septated effusion, but there is a high rate of recurrent symptomatic loculation (**Ungraded**)

Recommendations

Due to the lack of supporting evidence, no recommendations can be made on the use of intrapleural enzymes or surgery for treating adults with malignant pleural effusion and septated effusion (on radiology).

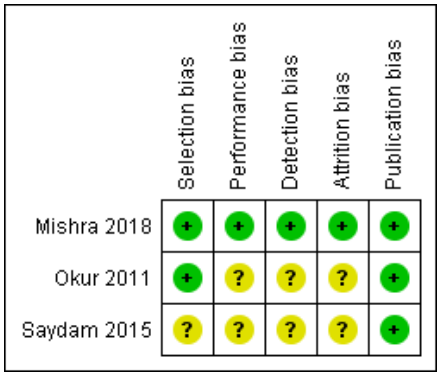
Good Practice Points

- ✓ Intrapleural fibrinolytics can be considered in highly selected symptomatic patients with MPE and septated effusion to try to improve breathlessness
- ✓ Intrapleural fibrinolytics may be used in patients with malignant pleural effusion and septated effusion and an indwelling pleural catheter (IPC) to improve drainage if flushing the IPC with normal saline or heparin saline does not improve drainage
- ✓ Surgery can be considered for palliation of symptoms in a minority of patients with significantly septated MPE and associated symptoms and otherwise good prognosis and performance status

Research Recommendations

- Further research is needed into the use of intrapleural fibrinolytics to manage symptomatic loculations in patients with septated malignant pleural effusion, especially in the ambulatory patient group
- There is a need for research to investigate the surgical management of patients with septated malignant pleural effusion

Risk of bias summary



GRADE analysis

For adults with malignant pleural effusion and septated effusion (on radiology), are intrapleural enzymes better than no treatment at improving clinical outcomes?

Population: Adults aged 18+ with malignant pleural effusion and septated effusion (on radiology)

Intervention: Intrapleural enzymes

Comparator: No treatment

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			No treatment	Intrapleural enzyme	
Pleurodesis rate	133 (3 studies)	RR 0.76 (0.47 to 1.23)	**377 per 1000**	**287 per 1000** (177 to 464)	⨁◯◯◯ **VERY LOW** [a,b,c]
Breathlessness	103 (2 studies)	RR 0.58 (0.35 to 0.98)	**480 per 1000**	**278 per 1000** (168 to 470)	⨁◯◯◯ **VERY LOW** [a,b,c,d]

CI: Confidence interval

Explanations

a. High risk of bias in two studies
b. Some inconsistency, I^2 >50%
c. Some imprecision, wide CIs, crosses one MID
d. Downgraded as one study gave oxygen as a surrogate for breathlessness

References

1. Mishra EK, Clive AO, Wills GH, et al. Randomized controlled trial of urokinase versus placebo for nondraining malignant pleural effusion. *Am J Respir Crit Care Med.* 2018;197(4):502-508.
2. Saydam O, Karapinar K, Gokce M, et al. The palliative treatment with intrapleural streptokinase in patients with multiloculated malignant pleural effusion: a double-blind, placebo-controlled, randomized study. *Medical oncology (northwood, london, england).* 2015;32(6):612.
3. Okur E, Baysungur V, Tezel C, Ergene G, Okur HK, Halezeroglu S. Streptokinase for malignant pleural effusions: a randomized controlled study. *Asian Cardiovasc Thorac Ann.* 2011;19(3-4):238-243.
4. Thomas R, Piccolo F, Miller D, et al. Intrapleural fibrinolysis for the treatment of indwelling pleural catheter-related symptomatic loculations: a multicenter observational study. *Chest.* 2015;148(3):746-751.

Question Protocols

1. Intrapleural enzymes versus surgery

Field	Content
Review Question	For adults with malignant pleural effusion and septated effusion (on ultrasound or CT), are intrapleural enzymes better than surgery at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	For patients with symptomatic septated MPE, is giving intrapleural enzymes (tPA/Dnase, urokinase, streptokinase) better than surgical management?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and septated effusion (on ultrasound or CT)
Eligibility criteria – intervention(s)	Intrapleural enzymes
Eligibility criteria – comparators(s)	Surgical drainage or intervention
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	Mesothelioma Non-mesothelioma
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	We know that symptomatic septated MPE is difficult to manage and caused deceased QoL for patients. How to manage these patients and the role of intrapleural drugs is not known and will be the focus of this question

2. Intrapleural enzymes versus no treatment

Field	Content
Review Question	For adults with malignant pleural effusion and septated effusion (on radiology), are intrapleural enzymes better than no treatment at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	The standard treatment for patients with symptomatic septated MPE is no treatment, but is treatment with intrapleural enzymes (tPA/Dnase, urokinase, streptokinase) better at improving patient clinical outcomes
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and septated effusion (on ultrasound or CT)
Eligibility criteria – intervention(s)	Intrapleural enzymes
Eligibility criteria – comparators(s)	No treatment
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
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Rationale / context – what is known	We know that symptomatic septated MPE is difficult to manage and caused deceased QoL for patients. How to manage these patients and the role of intrapleural drugs is not known and will be the focus of this question