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 ............................................................................................................ 2
  Background.................................................................................................................................................... 2
  Outcomes....................................................................................................................................................... 2
  Evidence Review............................................................................................................................................ 2
    1.  Intrapleural enzymes versus surgery ................................................................................................. 2
    2.  Intrapleural enzymes versus no treatment ....................................................................................... 2
  Evidence Statements ..................................................................................................................................... 3
  Recommendations ......................................................................................................................................... 3
  Good Practice Points ..................................................................................................................................... 4
  Research Recommendations......................................................................................................................... 4

Risk of bias summary ..................................................................................................................... 4

GRADE analysis ...................................................................................................................................... 4

References................................................................................................................................................. 5

Question Protocols .............................................................................................................................. 6
  1.  Intrapleural enzymes versus surgery ................................................................................................. 6
  2.  Intrapleural enzymes versus no treatment ....................................................................................... 8
Question Evidence Review

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?

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 et 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

<table>
<thead>
<tr>
<th>Selection bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Attrition bias</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra 2018</td>
<td>★★</td>
<td>★★</td>
<td>★★</td>
<td>★</td>
</tr>
<tr>
<td>Okur 2011</td>
<td>★</td>
<td>★★</td>
<td>★</td>
<td>★★</td>
</tr>
<tr>
<td>Saydam 2015</td>
<td>★</td>
<td>★★</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleurodesis rate</td>
<td>133 (3 studies)</td>
<td>RR 0.76 (0.47 to 1.23)</td>
<td>377 per 1000 (177 to 464)</td>
<td>★★★★★ VERY LOW ab,c</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>103 (2 studies)</td>
<td>RR 0.58 (0.35 to 0.98)</td>
<td>480 per 1000 (168 to 470)</td>
<td>★★★★★ VERY LOW ab,c,d</td>
</tr>
</tbody>
</table>

CI: Confidence interval

Explanations

a. High risk of bias in two studies
b. Some inconsistency, I² >50%
c. Some imprecision, wide CIs, crosses one MID
d. Downgraded as one study gave oxygen as a surrogate for breathlessness
References


**Question Protocols**

1. **Intrapleural enzymes versus surgery**

<table>
<thead>
<tr>
<th>Field</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review Question</td>
<td>For adults with malignant pleural effusion and septated effusion (on ultrasound or CT), are intrapleural enzymes better than surgery at improving clinical outcomes?</td>
</tr>
<tr>
<td>Type of review question</td>
<td>Intervention review</td>
</tr>
<tr>
<td>Objective of the review</td>
<td>For patients with symptomatic septated MPE, is giving intrapleural enzymes (tPA/Dnase, urokinase, streptokinase) better than surgical management?</td>
</tr>
<tr>
<td>Eligibility criteria – population / disease / condition / issue / domain</td>
<td>Adults (18+) with malignant pleural effusion and septated effusion (on ultrasound or CT)</td>
</tr>
<tr>
<td>Eligibility criteria – intervention(s)</td>
<td>Intrapleural enzymes</td>
</tr>
<tr>
<td>Eligibility criteria – comparators(s)</td>
<td>Surgical drainage or intervention</td>
</tr>
</tbody>
</table>
| 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 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection process – duplicate screening / selection / analysis</td>
<td>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</td>
</tr>
</tbody>
</table>
| 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**

<table>
<thead>
<tr>
<th>Field</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review Question</strong></td>
<td>For adults with malignant pleural effusion and septated effusion (on radiology), are intrapleural enzymes better than no treatment at improving clinical outcomes?</td>
</tr>
<tr>
<td><strong>Type of review question</strong></td>
<td>Intervention review</td>
</tr>
<tr>
<td><strong>Objective of the review</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Eligibility criteria – population / disease / condition / issue / domain</strong></td>
<td>Adults (18+) with malignant pleural effusion and septated effusion (on ultrasound or CT)</td>
</tr>
<tr>
<td><strong>Eligibility criteria – intervention(s)</strong></td>
<td>Intrapleural enzymes</td>
</tr>
<tr>
<td><strong>Eligibility criteria – comparators(s)</strong></td>
<td>No treatment</td>
</tr>
</tbody>
</table>
| **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 |
<table>
<thead>
<tr>
<th>Selection process – duplicate screening / selection / analysis</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data management (software)</td>
<td>RevMan5 Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler Quality of evidence assessment Gradepro Recommendations</td>
</tr>
<tr>
<td>Information sources – databases and dates</td>
<td>MEDLINE, Embase, PubMed, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present</td>
</tr>
<tr>
<td>Methods for quantitative analysis – combining studies and exploring (in)consistency</td>
<td>If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in ‘BTS Guideline Process Handbook – Intervention Review’)</td>
</tr>
<tr>
<td>Rationale / context – what is known</td>
<td>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</td>
</tr>
</tbody>
</table>