INTRAPLEURAL FIBRINOLYTIC THERAPY VERSUS PLACEBO IN THE TREATMENT OF ADULT PARAPNEUMONIC EFFUSIONS

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ABSTRACT

Background: Parapneumonic effusion is a type of pleural effusion that arises as a result of a pneumonia. It can occur in 57% of pneumonia cases in adults. Current guidelines recommend that if chest tube drainage is ineffective, then surgical procedures should be first line management. Morbidity and mortality rate of surgical intervention are on concern. Less invasive therapies still need to be considerable clinical utility. Intrapleural Fibrinolytic agents have been used safely and effectively for complicated parapneumonic effusion but its role in parapneumonic effusion is still unknown.
Method: Literature search was performed on the PubMed, Cochrane Library, Proquest, Scopus, and EBSCO Host. Inclusion criteria of this literature searching was meta analysis, systematic review, and randomized control trial articles, articles in English or Indonesian, adult with parapneumonic effusions, and compare of fibrinolytic agents with placebo. The exclusion criteria was animal and in vitro research. Critical appraisal was assessed using FAITH tool.
Result: Three meta analysis included in this study. All of the studies concluded that there is no evidence intrapleural fibrinolytic therapy better than placebo to prevent mortality in adult with parapneumonic effusions. Even though, it is associated with reduction in surgical intervention and overall treatment failure.
Conclusion: Fibrinolytic therapy is potentially beneficial in the management of parapneumonic effusions in the adult population. Although there is insufficient evidence to support the routine use of this therapy for all parapneumonic effusions. Fibrinolytic therapy may be considered in patients with loculated pleural effusions, because it may prevent the need for surgical intervention.

Keywords: Parapneumonic effusion, Intrapleural fibrinolytic, mortality

ABSTRAK

Latar belakang: efusi parapneumonik merupakan jenis dari efusi pleura yang timbul akibat pneumonia. Kondisi ini terjadi pada 57% kasus pneumonia pada dewasa. Panduan yang ada saat ini merekomendasikan bahwa apabila pemasangan chest tube tidak efektif, dapat dilakukan prosedur bedah sebagai langkah selanjutnya. Morbiditas dan mortalitas dari prosedur bedah perlu dipertimbangkan dalam melakukan tatalaksana. Oleh sebab itu, diperlukan alternatif terapi yang bersifat non invasif. Fibrinolitik intrapleural sudah digunakan secara aman dan efektif pada komplikasi efusi parapneumonik, akan tetapi perannya pada efusi parapneumonik masih tidak diketahui
Metode: penelusuran literatur dilakukan pada PubMed, Cochrane Library, Proquest, Scopus, dan EBSCO Host. Kriteria inklusi yang digunakan adalah meta analisis, review sistematik, uji klinis terkontrol acak, artikel dalam bahasa inggris atau indonesia, pasien dewasa dengan efusi parapneumonik, dan membandingkan fibrinolitik dengan plasebo. Kriteria eksklusinya adalah penelitian pada hewan dan invitro. Penilaian kritis dilakukan dengan FAITH tool.
Hasil: tiga meta analisis tercakup dalam tulisan ini. Seluruh meta analisis berkesimpulan bahwa tidak terdapat bukti yang cukup bahwa fibrinolitik intrapleura lebih baik dibandingkan dengan plasebo dalam mencegah mortalitas pada dewasa dengan efusi parapneumonik, akan tetapi berhubungan dengan penurunan kebutuhan intervensi bedah dan gagal terapi.
Kesimpulan: terapi fibrinolitik memiliki potensi manfaat pada manajemen efusi parapneumonik pada dewasa. Walaupun demikian, tidak terdapat cukup bukti untuk mneggunakan terapi ini secara rutin. Terapi fibrinolitik interapleura dapat dipertimbangkan pada pasien dengan efusi pleura berlokulasi karena dapat mencegah kebutuhan intervensi bedah di masa depan.

Kata kunci: efusi parapneumonik, fibrinolitik intrapleura, mortalitas

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INTRODUCTION

Parapneumonic effusion is a type of pleural effusion that arises as a result of a pneumonia. Parapneumonic effusion can progress from simple to complicated parapneumonic effusion. Alternately, it may present as a primary pleural infection which is without evidence of pneumonia. Parapneumonic effusion can occur in 57% of pneumonia cases in adults. It can progress to empyema in up to 10% of people, and mortality rates are approximately 20%. The incidence of pleural infection has increased with mortality rate greater than 30% in adults aged over 65 years.[1,2] The high morbidity and mortality are associated with increased hospital stays and medical expenses. The median hospital stay for parapneumonic effusion patients is 12 until 15 days, and 25% of patients remain in the hospital for 1 month or longer. More than $320 million per year combined medical care costs for parapneumonic effusion patient in the United Kingdom and United States.[3-5]

Not only become incidental and nonsignificant finding, parapneumonic effusion can become large and persistent. [1,6] Drainage via intercostal catheter is an appropriate therapy in parapneumonic effusion. But sometimes because of presence of loculations, intercostal catheter drainage is not effective. Loculations is formed by fibrinous material deposited in the fibrinopurulent phase of empyema. This condition can prevent drainage of infected pleural fluid. Because intercostal drainage is not effective, usually video assisted thoracoscopic or open surgery is required. Despite success rate of surgical intervention is high, morbidity and mortality rate of surgical intervention are on concern. Less invasive therapies still need to be considerable clinical utility.[1,7]

Intrapleural Fibrinolytic agents like streptokinase, alteplase, and recombinant plasminogen activator (rTPA) have been used safely and effectively for complicated parapneumonic effusion and empyema. During fibrinopurulent and purulent stage of empyema, there is an imbalance between fibrin activators and inhibitors. With elevated levels of plasminogen activator inhibitor (PAI-1) resulting from the presence of inflammation-induced tumour necrosis factor-alpha, interleukin 8 and transforming growth factor beta, as well as lower levels of endogenous tissue plasminogen activator. This condition results in pro fibrotic state causing deposition of fibrin forming loculations within the infected pleural space. Fibrinolytic agents activate plasmin and lysing fibrinous septations, after that improve pleural fluid drainage and clearing infection.[1,8]

Current guidelines recommend that if chest tube drainage is ineffective, then surgical procedures via video assisted thoracoscopic surgery or thoracotomy should be first line management for empyema and complicated parapneumonic effusion. Intrapleural fibrinolysis is not routinely used.[1,6,9] The purpose of this study is to conduct a evidence based case report to date comparing fibrinolytics with placebo to clarify their current role in the management of parapneumonic effusions.

CASE ILLUSTRATION

A 53-year-old male came to emergency department in our hospital with shortness of breath since two days before admission. Shortness of breath was felt continuously, worsen with flat position and physical activity, accompanied with pain in left ribs especially when inhaling, and he felt better when in sitting position. Since two weeks before admission, he starts coughing. Cough was accompanied with white phlegm. There was no history of fever, decreased body weight, and night sweat. He had no history of hypertension, diabetes, autoimmune disease, kidney disease, heart disease, liver disease, and no using of routine drugs before. There was no history of same complain, lung disease, hypertension, diabetes, autoimmune disease, kidney disease, heart disease, and liver disease in his family.

On physical examination, he was fully alert, with blood pressure 150/100 mmHg, heart rate 100 beats per minute, regular, respiration rate 27 times per minute, axilla temperature 36,6^{o}C, and peripheral oxygen saturation 99% with oxygen from nasal cannula three litres per minute. Patient feel more comfortable with sitting position. From lung examination, pattern of breathing is abdominothoracic, we could see asymmetrical chest expansion on the left side of thorax. There was the use of intercostal muscle, decreased tactile fremitus and dullness to percussion in left thorax. From auscultation, we found decreased vesicular sound of left lung, rhonchi were heard in both of lung. Heart examination and abdominal examination was within normal limit.

Laboratory examination showed leucocytosis (leucocyte count 15740/uL), hyponatremia (126 mEq/L), hypoalbuminemia (2,78 g/dL), increase in CRP (210,7 mg/L), and increase in procalcitonin (1,47 ng/mL). Electrocardiogram examination found normal result. There was pleural effusion in left lung found in chest x-ray. Thoracic ultrasonography showed loculated pleural in left hemithorax. Thoracic CT scan showed left pleural effusion with multiloculated pleural in lower-middle field of left hemithorax.

He was diagnoses with left parapneumonic effusion with loculated pleural, community acquired pneumonia, hyponatremia, hypertension, and hypoalbuminemia. Thoracentesis was done in emergency department. Two hundred millilitres of yellowish fluid were removed from left pleural space. Further aspiration of the fluid ended in failure. From pleural fluid laboratory examination, pleural fluid analysis showed leucocyte 25-30/large field view, epithelium 0-1/large field view, pleural fluid culture was sterile, gram staining was negative, tuberculosis PCR was negative, and adenosine deaminase (ADA) was 16 U/ml.

He was planned to have intrapleural fibrinolytics, but its effectiveness to prevent mortality is still unknown.

CLINICAL QUESTION

Based on case illustration, we formulated PICO and clinical question as follows:

Patient : Adult with parapneumonic effusions
Intervention : Intrapleural fibrinolytic
Comparison : Placebo
Outcome : Mortality

In adult with parapneumonic effusions, does intrapleural fibrinolytic therapy better than placebo to prevent mortality?

SEARCHING STRATEGY

We conducted literature search on five search engines, included PubMed, Cochrane library, Proquest, Scopus, and EBSCO. The searching strategy was described in table 1. Our search strategy was restricted by last 10 years of publication. Article eligible for critical appraisal should meet our inclusion criteria as follow: (1) meta analysis, systematic review, and randomized control trial articles (2) articles in English or Indonesian (3) adult with parapneumonic effusions (4) compare of fibrinolytic agents with placebo. The exclusion criteria in this literature searching was animal and in vitro research.

In search engines' result, screening of titles according to PICO, inclusion criteria, and exclusion criteria would be conducted. After that, if from the screening of titles, the articles were considered appropriate or uncertain, full text will be assessed. Critical appraisal would be performed in selected article.

Table 1. Searching strategy

Search engine	Search term
Pubmed	(((Parapneumonic effusions[MeSH Terms]) AND (Intrapleural fibrinolytic[MeSH Terms])) AND (placebo[MeSH Terms])) AND (mortality[MeSH Terms])
Cochrane library	Parapneumonic effusions AND Intrapleural fibrinolytic AND Placebo AND Mortality
Proquest	Parapneumonic effusions AND Intrapleural fibrinolytic AND Placebo AND Mortality (filter: academic journal)
Scopus	Parapneumonic effusions AND Intrapleural fibrinolytic AND Placebo AND Mortality

EBSCO Host	Parapneumonic effusions AND Intrapleural fibrinolytic AND Placebo AND Mortality

LITERATURE SEARCH

From literature searching, we retrieved 70 records. From title and abstract screening, we excluded 63 articles. Four articles were excluded because of duplication. Three articles were eligible for critical appraisal.

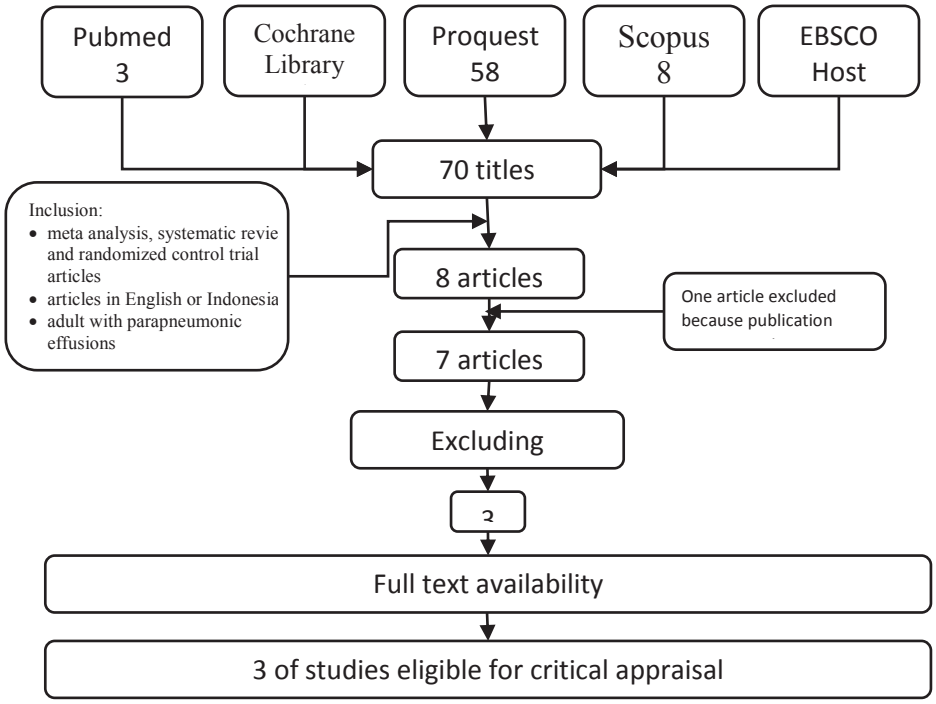


Figure 1. Literature search based on PRISMA flowchart

CHARACTERISTICS OF SELECTED STUDIES

Characteristics of domain, determinant, outcome, and study design are shown in table 1. All of the selected studies are meta analysis.

Table 2. Characteristics of selected studies

	Article 1
Author	Altmann ES, et al[1]
Title	Intrapleural fibrinolytic therapy versus placebo or a different fibrinolytic agent, in the treatment of adult parapneumonic effusions and empyema
Domain	Randomised controlled trials with participants older than 14 years presenting with either thoracic empyema or complicated parapneumonic effusions
Determinant	Intrapleural fibrinolytics versus placebo
Outcomes	Mortality, referral for thoracic surgery, overall treatment failure, serious adverse events
Design	Meta analysis
Sample size	twelve randomised controlled trials
	Article 2
Author	Nie W, et al[3]

Title	Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta analysis of randomized control trials
Domain	Randomised controlled trials with objectively diagnosed empyema or parapneumonic effusions, compare of fibrinolytic agents with placebo, and have a objective methods to assess clinical outcome
Determinant	Intrapleural fibrinolytics versus placebo
Outcomes	Need for surgical intervention. Length of stays, mortality rate, and severe side effect
Design	Meta analysis
Sample size	ten randomised controlled trials with total of 977 patients
	Article 3
Author	Janda S, et al[10]
Title	Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyema
Domain	Randomised controlled trials with adult participants (>19 years of age) with parapneumonic effusion or empyema and compare fibrinolytic or thrombolytic with placebo.
Determinant	Intrapleural fibrinolytics versus placebo
Outcomes	Treatment failure, surgical intervention, length of stay, and death
Design	Meta analysis
Sample size	ten randomised controlled trials with total of 977 patients

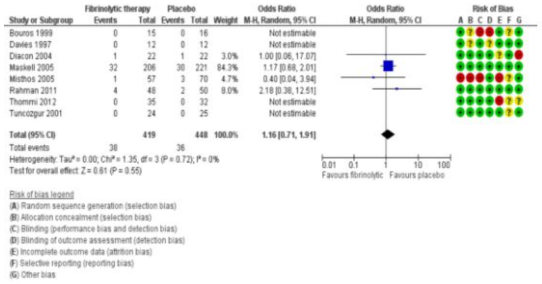
CRITICAL APPRAISAL

Critical appraisal was assessed using FAITH tool

Table 3. Critical appraisal of the studies

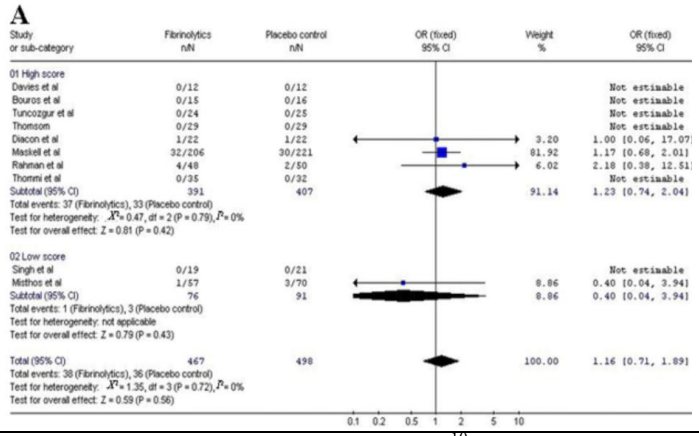
	Altman ES, et al[1]
Internal Validity	
Does the systematic review address a focused question (PICO)?	Yes **"*Types of participants*** *We included trials with participants older than 14 years presenting with either thoracic empyema or complicated parapneumonic effusions. We excluded studies on known tuberculous effusions and those on participants with malignancy, trauma or prior surgical intervention. We also excluded trials comparing fibrinolytic therapy with surgical therapies.* ***Types of interventions*** *1. Intrapleural fibrinolytics versus control* *a. Intrapleural streptokinase versus intrapleural normal saline* *b. Intrapleural urokinase versus intrapleural normal saline* *c. Intrapleural alteplase versus intrapleural normal saline* *2. Intrapleural streptokinase versus intrapleural urokinase* *3. Intrapleural alteplase versus intrapleural urokinase* ***Types of outcome measures*** *Primary outcomes* *1. Mortality* *2. Referral for thoracic surgery (open or thoracoscopic)* *3. Overall treatment failure, including mortality, thoracic surgery or referral for further fibrinolytic therapy* *4. Serious adverse events*"
... and use it to	Yes

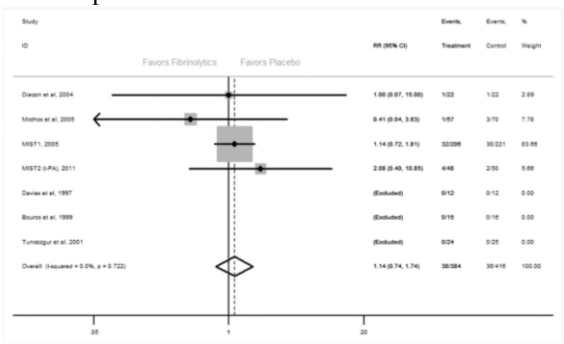
direct the search and select articles for inclusion?	"*Criteria for considering studies for this review included types of studies, types of participants, types of interventions, and types of outcome measures*"
Did the search find all the relevant evidence?	Yes *"The Cochrane Airways Information Specialist conducted searches in the following databases and trials registries.* *• Cochrane Airways Register via the Cochrane Register of Studies (CRS Web) (searched 28 August 2019);* *• Cochrane Central Register of Controlled Trials (CENTRAL; 2010, Issue 8) via the Cochrane Register of Studies (CRS Web)* *(searched 28 August 2019);* *• MEDLINE (Ovid) 1946 to December week 4 2017 (searched 28 August 2019);* *• Embase (Ovid) 1976 to week 2 2018 (searched 28 August 2019);* *• ClinicalTrials.gov (searched 28 August 2019);* *• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched 28 August 2019).* *We searched databases from their inception to the present, with no restriction on language of publication, or publication type. We handsearched conference abstracts via the CENTRAL database. We searched ClinicalTrials.gov and The WHO Trials portal for ongoing. We reviewed reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify other published and unpublished studies. Or unpublished trials."*
Have the studies been critically appraised?	Yes **"*Selection of studies*** *EA and IC independently reviewed titles and abstracts to identify all potential RCTs and obtained full-text versions of these articles. We reviewed online supplementary data where available. Cochrane language specialists reviewed studies in languages other than English for consideration of inclusion.*"
Did they only include high quality studies?	Yes **"*Data extraction and management*** *We extracted data for all included studies using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and standard templates and methods. Two out of three authors (EA, IC and SW), working independently, updated 'Risk of bias' assessments for all included studies in line with current Cochrane protocols.* ***Assessment of risk of bias in included studies*** *Two authors independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We resolved any disagreements by discussion. We assessed risk of bias according to the following domains.* *1. Random sequence generation* *2. Allocation concealment* *3. Blinding of participants and personnel* *4. Blinding of outcome assessment* *5. Incomplete outcome data* *6. Selective outcome reporting* *7. Other bias* *We graded each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for the judgment in the 'Risk of bias' table. We have summarized the 'Risk of bias' judgements across different studies for each of the domains*."
Have the results been totaled up with appropriate summary tables and plots?	Yes In summary tables and forest plot
...and heterogeneity between studies assessed and	Yes **"*Subgroup analysis and investigation of heterogeneity*** *We used the IL statistic to measure heterogeneity amongst the trials for each outcome.*"

explained?	
Result	
What measure was used, how large was the effect (could it have been due to chance)?	OR 1.16, 95% CI 0.71 to 1.91; 867 participants; IL = 0% There was no clear difference between the groups for this Outcome
How are the results presented?	In forest plot 

Nie W, et al[3]

Internal Validity	
Does the systematic review address a focused question (PICO)?	Yes P: empyema or parapneumonic effusions I: fibrinolytic agents C: placebo O: Mortality, need for thoracic surgery, durations of hospital stays and severe side effects associated with treatment
... and use it to direct the search and select articles for inclusion?	Yes "*Trials were included if they satisfied the following criteria: (i) RCT; (ii) objectively diagnosed empyema or parapneumonic effusions; (iii) comparison of fibrinolytic agents with placebo; and (iv) objective methods to assess clinical outcomes. We excluded trials for patients who had prior surgical intervention, posttraumatic infection and malignant effusion. Two investigators (FC Shao and WC Nie) independently evaluated studies for inclusion. Disagreements were referred to a third investigator (RF Zhang)*."
Did the search find all the relevant evidence?	Yes *"Medline (using PubMed as the search engine), Web of Science and Ovid were searched to identify suitable studies conducted prior to June 10, 2012; no start date limit was applied. The search terms used were empyema OR parapneumonic OR pleural effusion OR pleural infection OR intrapleural AND fibrinolysis OR fibrinolytic OR streptokinase OR urokinase OR tissue* *plasminogen activator OR t-PA in combination with randomized controlled trial OR controlled clinical trial OR RCT. Articles were also identified by using the related articles function in PubMed, and the references in identified articles were searched manually. If needed, we contacted the papers' authors for further study details. We attempted to extend our search to any language of publication and limited our search to studies that involved humans only. Conference abstracts to journal editors were excluded because of their limited data."*
Have the studies been critically appraised?	Yes *"Two reviewers (RF Zhang and WC Nie) independently assessed allocation concealment and the likelihood of bias to determine the methodological quality of the included trials. Trials were scored according to the allocation of concealment (14) and Jadad scores (26). Any disagreement between reviewers as resolved by consensus."*
Did they only include high quality studies?	No but they separated results from high quality and low quality studies based on their score
Have the results been totaled up with appropriate summary tables and plots?	Yes in summary tables and forest plots

...and heterogeneity between studies assessed and explained?	Yes "*Heterogeneity was analyzed with the Q statistic (P < 0.1 was considered significant). A random effects model was used if the Q statistic was significant; otherwise, we used a fixed effects model. Subgroup analysis was used to assess the source of heterogenity.*"
Result	
What measure was used, how large was the effect (could it have been due to chance)?	*"The pooled estimate of the OR for mortality from all 10 trials was not statistically significant (OR = 1.16; 95% CI: 0.71–1.89). These results showed that intrapleural fibrinolysis did not reduce mortality. This estimate was determined using a fixed effects model because heterogeneity was not present by Q test (χ2 = 1.35, P = 0.72, I2 = 0%). Subgroup analyses were also done based on the trial quality and different fibrinolytic agents used. Consistent with the total estimates, neither high quality (Jadad score ≥3; OR = 1.23; 95% CI: 0.74–2.04) nor low quality (Jadad score <3; OR = 0.40; 95% CI: 0.04–3.94) trials found any reductions in mortality (Fig. 3A). Both t-PA (OR = 2.18; 95% CI: 0.38–12.51) and streptokinase (OR = 1.09; 95% CI: 0.65–1.82) did not reduce mortality.*"
How are the results presented?	In forest plot  **A** Study or sub-category / Fibrinolytics n/N / Placebo control n/N / OR (fixed) 95% CI / Weight % / OR (fixed) 95% CI 01 High score Davies et al 0/12 0/12 Not estimable Bouros et al 0/15 0/16 Not estimable Tuncozgur et al 0/24 0/25 Not estimable Thomsom 0/29 0/29 Not estimable Diacon et al 1/22 1/22 3.20 1.00 [0.06, 17.07] Maskell et al 32/206 30/221 81.92 1.17 [0.68, 2.01] Rahman et al 4/48 2/50 6.02 2.18 [0.38, 12.51] Thormi et al 0/35 0/32 Not estimable Subtotal (95% CI) 391 407 91.14 1.23 [0.74, 2.04] Total events: 37 (Fibrinolytics), 33 (Placebo control) Test for heterogeneity: χ^2 = 0.47, df = 2 (P = 0.79), I^2 = 0% Test for overall effect: Z = 0.81 (P = 0.42) 02 Low score Singh et al 0/19 0/21 Not estimable Misthos et al 1/57 3/70 8.86 0.40 [0.04, 3.94] Subtotal (95% CI) 76 91 8.86 0.40 [0.04, 3.94] Total events: 1 (Fibrinolytics), 3 (Placebo control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.79 (P = 0.43) Total (95% CI) 467 498 100.00 1.16 [0.71, 1.89] Total events: 38 (Fibrinolytics), 36 (Placebo control) Test for heterogeneity: χ^2 = 1.35, df = 3 (P = 0.72), I^2 = 0% Test for overall effect: Z = 0.59 (P = 0.56) 0.1 0.2 0.5 1 2 5 10
Janda S, et al[10]	
Internal Validity	
Does the systematic review address a focused question (PICO)?	Yes P: adults (>19 years) with parapneumonic effusions and empyemas. I: Fibrinolytics C: Placebo O: Treatment failure (surgical intervention or death), surgical intervention, duration of hospital stay, death
... and use it to direct the search and select articles for inclusion?	Yes "*We only included studies of adults (>19 years of age) that were placebo controlled. Studies with primarily tuberculous effusions were excluded.*"
Did the search find all the relevant evidence?	Yes "*The systematic review and meta-analysis was performed according to the published recommendations and checklist of the Preferred Reporting Items for Systematic Reviews and Meta analysis (PRISMA) statement. Searches were conducted on MEDLINE (inception to October 2011), EMBASE (inception to October 2011), PapersFirst (inception to October 2011), and the Cochrane collaboration and the Cochrane Register of controlled trials for relevant studies. The following key terms were used: "pleural effusion" or "parapneumonic" or "empyema" or intrapleural" or "pleur*" AND "fibrinolytic" or "antithrombotic" or "thrombolytic" or "streptokinase" or "urokinase," "alteplase" or "t-PA" or "DNase." All searches were limited to "humans" and "randomized controlled trials." We only included studies of adults (>19 years of age) that were placebo controlled. Studies with primarily tuberculous effusions were excluded. We identified additional studies by searching the bibliographies of retrieved articles. Two independent reviewers (S. J. and J. S.) performed the literature search.*"
Have the studies been critically	Yes "*All studies that appeared to fi t the inclusion criteria were identified for full review by two*

appraised?	*reviewers (S. J. and J. S.). Each reviewer independently selected studies for inclusion in the review. Disagreement between the two extracting authors was resolved by consensus. The methodologic quality of the selected studies was graded independently by two reviewers (S. J. and J. S.) using two methods: the Cochrane concealment of allocation approach and the Jadad criteria. The Cochrane approach assesses allocation concealment using the following principles: grade A is adequate concealment, grade B is uncertain concealment, and grade C is clearly inadequate concealment. In addition, each study was assessed using a previously validated 0 to 5 scale described by Jadad. The Jadad Scale determines the quality of clinical trials based on study randomization, the presence of double blinding, the description of withdrawals, and the process of randomization and blinding. Disagreement between the two extracting authors was resolved by consensus.*"
Did they only include high quality studies?	Yes All of the included study has Jadad Score 5, which is high quality study
Have the results been totaled up with appropriate summary tables and plots?	Yes in summary tables and forest plots
...and heterogeneity between studies assessed and explained?	Yes "*We assessed binary outcomes as RRs with 95% CIs. In the absence of significant heterogeneity (P> 0.05), a fixed-effects model was used, whereas in the presence of significant heterogeneity (P > 0.05), the DerSimonian and Laird random-effects model was used. Heterogeneity between studies was explored using the I2 statistic*."
Result	
What measure was used, how large was the effect (could it have been due to chance)?	There was no difference in death (RR, 1.14; 95% CI, 0.74-1.74).
How are the results presented?	In forest plot 

DISCUSSION

Plasminogen activators like tissue plasminogen activator, urokinase, desmoteplase, streptokinase, staphylokinase work by activating plasminogen into the active form plasmin. Plasmin digests selectively only fibrin to form soluble fibrin degradation products if it is bound to the surface of a fibrin clot. Because the recognition site of plasmin is sterically hindered by bound fibrin, this process cannot be inhibited by α2-antiplasmin or α2-macroglobulin. Plasmin can digest fibrinogen and factor VIII instead of fibrin if it is generated in circulating blood. This process is inhibited by α2-antiplasmin or α2-macroglobulin. Fibrinogenolysis and subsequent plasminemia caused by inhibition often lead to extensive bleeding complications.[11]

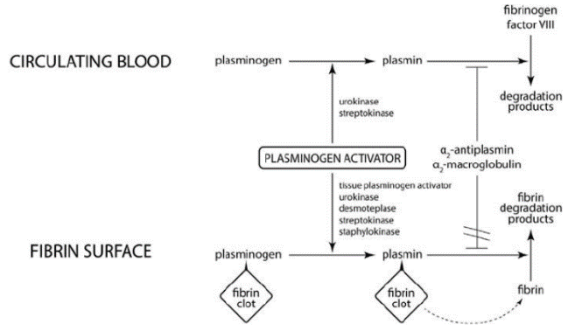


Figure 4.1. Principles of thrombolysis[11]

Altmann, et al analyses four outcomes: overall mortality, reduction in surgical intervention, overall treatment failure, and increase in adverse effect. No evidence in overall mortality with fibrinolytic versus placebo (OR 1.16 95%CI 0.71 to 1.91 8 studies, 867 participants; IL = 0%; moderate certainty of evidence) and increase in adverse effect (OR 1.28, 95%CI 0.36 to 4.57; low certainty of evidence). Although, there are evidence of reduction in surgical intervention (OR 0.37, 95% CI 0.21 to 0.68; 8 studies, 897 participants; IL = 51%; low certainty of evidence) and overall treatment failure (OR0.16, 95% CI 0.05 to 0.58; 7 studies, 769 participants; IL = 8%; very low certainty of evidence, with evidence of significant heterogeneity).[1]

Nie, et al analyses ten trials with a total of 977 patients were included. Compared with a placebo, intrapleural fibrinolytic therapy decreased the OR for surgical intervention [OR = 0.24; 95% confidence interval (CI): 0.10–0.60] and the length of hospital stays (weighted mean difference = −6.47; 95% CI: −8.87, −4.08). Intrapleural fibrinolysis was associated with a non-significant reduction in mortality rate (OR = 1.16; 95% CI: 0.71–1.89) and a non-significant increase in severe side effects (OR = 1.92; 95% CI: 0.87–4.21).[3]

Janda, et al analyses seven randomized controlled studies (total number of patients, 801) comparing fibrinolytic therapy with placebo. Fibrinolytic therapy was beneficial for the outcomes of treatment failure (surgical intervention or death) (RR, 0.50; 95%CI, 0.28-0.87) and surgical intervention alone (RR, 0.61; 95% CI, 0.45-0.82). There was no difference in mean duration of hospital stay (standard mean difference, 20.69;95% CI, 21.54-0.16) or death (RR, 1.14; 95% CI, 0.74-1.74).[10]

All of the studies concluded that there is no evidence intrapleural fibrinolytic therapy better than placebo to prevent mortality in adult with parapneumonic effusions. Even though, intrapleural fibrinolytic is associated with reduction in surgical intervention and overall treatment failure with low certainty of evidence because of significant heterogeneity.

Fibrinolytic therapy is potentially beneficial in the management of parapneumonic effusions in the adult population. Although there is insufficient evidence to support the routine use of this therapy for all parapneumonic effusions, fibrinolytic therapy may be considered in patients with loculated pleural effusions, because it may prevent the need for surgical intervention.

CONCLUSION

- In patients with complicated infective pleural effusion, there is no evidence of intrapleural fibrinolytic can prevent mortality.
- Intrapleural fibrinolytic therapy was associated with a reduction in the requirement for surgical intervention and overall treatment failure but with low certainty of evidence.
- Intrapleural fibrinolytic may be a reasonable therapy in patients with empyema or complex parapneumonic effusion, particularly in patients in whom surgery is contraindicated or in patients with loculated pleural effusions, because it may prevent the need for surgical intervention.

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