Original Article

trd Tuberculosis & Respiratory Diseases

Intrapleural Fibrinolysis with Urokinase versus Alteplase in Complicated Pleural Effusions and Empyema: A Prospective Randomized Controlled Trial

https://doi.org/10.4046/trd.2022.0168
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:378-385

Sudipt Adhikari, M.B.B.S., M.D.[1], Vikas Marwah, M.D.[1], Robin Choudhary, M.D.[1], Indermani Pandey, M.D.[1], Tentu Ajai Kumar, M.D.[1], Virender Malik, M.D., D.N.B., D.M.[2], Arpita Pemmaraju, M.D.[3], Shrinath Vasudevan, M.D.[1] and Suraj Kapoor, M.D.[4]

Departments of [1]Pulmonary, Critical Care and Sleep Medicine, [2]Radiology, [3]Pathology, Army Institute of Cardiothoracic Sciences (AICTS), Pune, [4]Department of Community Medicine, Armed Forces Medical College (AFMC), Pune, India

Address for correspondence
Robin Choudhary, M.D.
Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardiothoracic Sciences (AICTS), Pune, Maharashtra, India
Phone 96-73300582
E-mail robinch19@gmail.com
Received Jan. 10, 2023
Revised Mar. 26, 2023
Accepted Feb. 27, 2024
Published online Mar. 7, 2024

Abstract

Background: Intrapleural fibrinolytic therapy (IPFT) has been used as an effective agent since 1949 for managing complicated pleural effusion and empyema. Several agents, such as streptokinase, urokinase (UK), and recombinant tissue plasminogen activator (rt-PA), have been found to be effective with variable effectiveness. However, a head-to-head controlled trial comparing the efficacy of the most frequently used agents, i.e., UK and rt-PA (alteplase) for managing complicated pleural effusion has rarely been reported.

Methods: A total of 50 patients were randomized in two intervention groups, i.e., UK and rt-PA. The dose of rt-PA was 10 mg, and that of UK was 1.0 lac units. UK was given thrice daily for 2 days, followed by clamping to allow the retainment of drugs in the pleural space for 2 hours. rt-PA was instilled into the pleural space twice daily for 2 days, and intercostal drainage was clamped for 1 hour.

Results: A total of 50 patients were enrolled into the study, of which 84% (n=42) were males and 16% (n=8) were females. Among them, 30 (60%) patients received UK, and 20 (40%) patients received alteplase as IPFT agents. The percentage of mean± standard deviation changes in pleural opacity was –33.0%±9.9% in the UK group and –41.0%±14.9% in the alteplase group, respectively (p=0.014). Pain was the most common adverse side effect, occurring in 60% (n=18) of the patients in the UK group and in 40% (n=8) of the patients in the alteplase group (p=0.24), while fever was the second most common side effect. Patients who reported early (within 6 weeks of onset of symptoms) showed a greater response than those who reported late for the intervention.

Conclusion: IPFT is a safe and effective option for managing complicated pleural effusion or empyema, and newer agents, such as alteplase, have greater efficacy and a similar adverse effect profile when compared with conventional agents, such as UK.

Keywords: Complicated Pleural Effusion; Empyema; Intrapleural Fibrinolysis; Urokinase; Recombinant Tissue Plasminogen Activator; Alteplase

Introduction

Thoracic empyema continues to be a significant cause of morbidity, especially in developing countries. Pulmonary infections, including community-acquired pneumonia, bronchiectasis, and lung abscess, are the most prevalent cause of thoracic empyema in developed countries, followed by surgical trauma[1]. In contrast, studies from India have revealed that tuberculosis accounts for a large number of empyema cases (38.6%)[2].

In empyema and complicated parapneumonic effusions (CPE), leucocytes sequestrate into the infected pleural space and secrete several permeable factors causing spillage of fibrinogen into the pleural space. Fibrinogen is then converted to fibrin, which adheres to the tissue surface, which traps the pathogenic microorganism. However, this entrapment prevents host defence mechanisms and antibiotics from reaching the site of infection. Infected pleural fluid has been shown to have low fibrinolytic activity and increased concentrations of plasminogen activator inhibitors[1-3].

Tillet and Sherry[4] first demonstrated the use of fibrinolytic therapy in 1949 as a treatment for empyema[3,4]. Fibrinolytic therapy was reintroduced by Bergh et al.[5] in 1977, and they used a more refined form of streptokinase (STK)[6,7]. Many trials and reports have shown the effectiveness of fibrinolytic agents for the treatment of empyema/CPE[6,8]. However, these were small trials and case series with success rates ranging from 38% to 100%[6,7,9].

Intrapleural fibrinolytic therapy (IPFT) is frequently administered to patients with CPE or empyema in whom antibiotic therapy and initial drainage fail[10-12]. It is also a suitable option for patients who are not candidates for or do not want to undergo surgery[13]. The rationale for this approach is that this strategy reduces the need for surgery and shortens the duration of hospitalization[3,11].

Urokinase (UK) was effective in a randomized trial of patients with multiloculated pleural effusions[14,15]. Patients in the intervention group with UK showed significantly more drainage volume of pleural fluid, required less surgical referral, and required fewer days in the hospital. Intrapleural recombinant tissue plasminogen activator (rt-PA) has been successfully administered in patients with complicated parapneumonic pleural effusion and empyema.

The landmark multicenter intrapleural sepsis trial (MIST2) published in 2011 included a comparison with intrapleural recombinant human DNase, a potential treatment for pleural infection that may help prevent septate formation and decreased viscosity by destroying extracellular DNA[11]. The blinded 2-by-2 factorial trial randomly assigned 210 patients with pleural disease to receive a 3-day study treatment using double placebo, rt-PA and placebo, DNase and placebo, or rt-PA and DNase. The combined intrapleural rt-PA and DNase therapy reduced the hospital stay length, decreased the need for thoracic surgery, and produced a more considerable improvement in pleural opacity on day seven relative to double placebo[16].

After the MIST2 study, no other randomized trial has been performed in this field. In our study, we aimed to compare the efficacy of UK versus rt-PA (alteplase) as intrapleural fibrinolytic agents for the management of complicated pleural effusion.

Materials and Methods

To evaluate the efficacy of UK versus rt-PA (alteplase) as intrapleural fibrinolytic agents for the management of complicated pleural effusion.

1. Objectives

1) Primary objective

The primary objective of this study was to compare the outcomes of UK vs. Alteplase as intrapleural fibrinolytic agents at a tertiary care Respiratory Center in Western Maharashtra.

2) Secondary objective

The secondary objective was to evaluate the safety profile of Intrapleural fibrinolytic agents.

2. Study design

This randomized trial was conducted at our center from December 2019 to June 2021. Ethical and regulatory approval was obtained before the recruitment of subjects. The study was approved by the Institutional ethics committee of Armed Forces Medical College (IEC/Oct/2019 dated 19/10/2019) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

3. Patients

Eligibility criteria were clinical and radiological evidence of infection and loculated pleural effusion that was either macroscopically purulent, positive on culture for bacterial infection, or positive for bacteria on Gram staining, or pleural fluid that had a lactate dehydrogenase (LDH) level of more than 1,000 on biochemical evaluation. In the study group, empyema included both tuberculous and bacterial empyema.

Exclusion criteria were age less than 18 years, pre-

viously treatment with IPFT, known sensitivity to UK or rt-PA, any history of bleeding diathesis, pregnancy or lactation, broncho-pleural fistula, and life expectancy of less than 3 months.

4. Randomization

After obtaining written informed consent from patients, they were assigned to a study group using randomization by the date of admission. The patients admitted on an odd date were assigned to the first group, and the remaining patients were assigned to the second group. We followed a double blinding method as neither the patient nor the doctor had any knowledge about the drug allocated to the patients. The measured dose of tissue plasminogen activator (t-PA) or UK was issued to the physician in unmarked 50 mL syringes. The two study treatment groups were t-PA and UK. Placebo groups were not included as both the drugs had proven efficacy compared to placebo, which was demonstrated in previous studies.

The dose of rt-PA was 10 mg, and that of UK was 1.0 lac units. UK was given thrice daily for 2 days, followed by clamping to allow the retainment of drugs in the pleural space for 2 hours. rt-PA was instilled into the pleural space twice daily for 2 days, and intercostal drainage was clamped for 1 hour.

The relevant independent variables were collected during the study period and were stored as raw data sheets in Excel, word.doc, and PDF formats. Later, data were refined and analyzed during the analysis phase, and co-relation, association, and significance were calculated using STATA software version 3 (StataCorp., College Station, TX, USA). The results were then presented in the Figure 1.

Results

A total of 50 patients were enrolled into the study. Among them, 84% (n=42) were males and 16% (n=08) were females. The majority of the patients belonged to the young age group (between 20 and 30 years), which led to skewing of the age distribution graph to the right. However, this was an expected phenomenon as the majority of the clientele in our hospital are young individuals.

The causes of empyema included tuberculous (60%) and bacterial empyema (40%). Among them, 30 (60%) patients received UK, and 20 (40%) patients received alteplase as IPFT agents. The baseline demography, radiological, and biochemical parameters are summarized in Table 1.

Parameters, such as pre-intervention radiological fea-

Figure 1. Framework of the study.

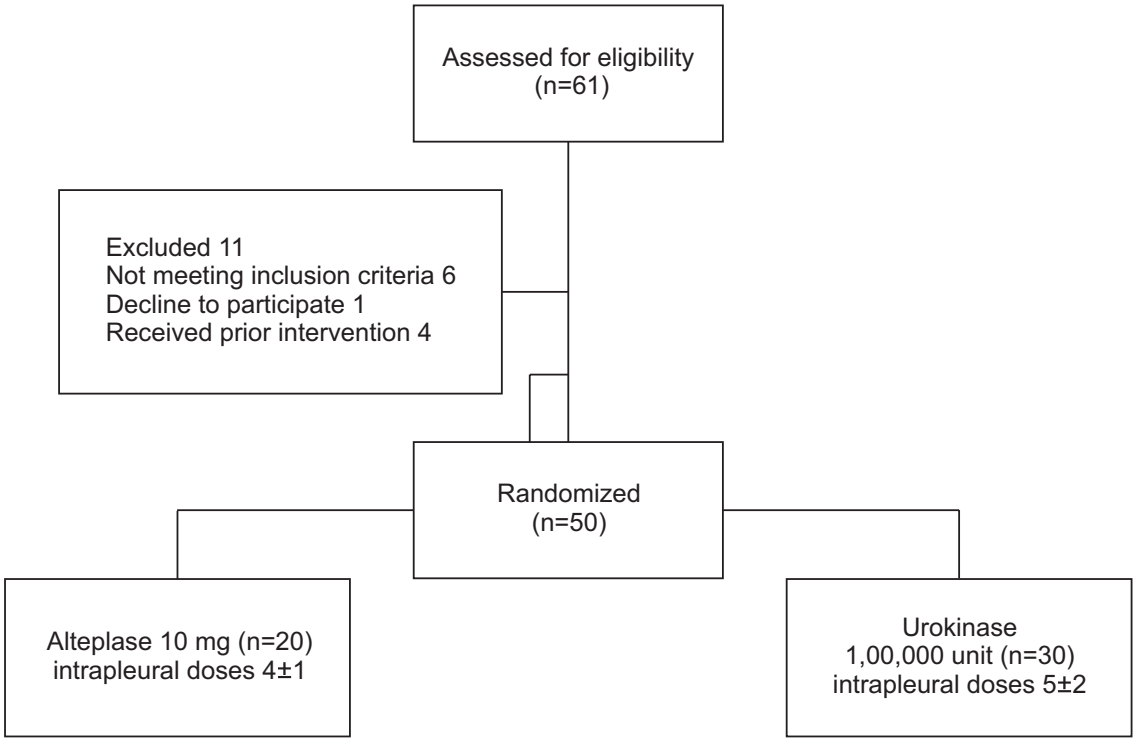

Table 1. Baseline characteristic of the patients according to the study group

Characteristic	rt-PA	Urokinase
Total no. (% of subjects)	20 (40)	30 (60)
Male sex	20	22
Age, yr	24 (21–37)	21 (19–24)
Hemithorax occupied with pleural fluid, %	33.5±18.2	27.3±14.4
Lactate dehydrogenase in pleural fluid, IU/L	2,075±795	1,730±733
Initial volume of fluid, mL	1,758±995	1,887±1,091
Duration of symptoms before intervention, wk	3 (1–6)	5 (3–7)

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
rt-PA: recombinant tissue plasminogen activator.

Table 2. Table showing comparison of pleural fluid clearance in both the arms between urokinase and alteplase

	Drugs	No.	Changes of hemithorax area occupied by pleural fluid, %	p-value
Clearance	UK	30	−33.00±9.9	0.014
	rt-PA	20	−42.00±14.9	

Values are presented as mean±standard deviation.
rt-PA: recombinant tissue plasminogen activator.

tures, initial volume of the pleural fluid, and pleural fluid LDH, were similar in both groups. The median value of age and interval of symptoms to the intervention were comparable.

1. Primary endpoints

The primary outcome was the change in pleural opacity, measured as the percentage of the areas of pre-treatment hemithorax occupied by effusion, on chest radiography and on completion of the therapy. The area of pleural opacity and hemithorax was measured digitally, and the response was quantified as maximum (near normal chest radiograph), moderate (50% to 80% clearance of pleural opacities) and minimal (<50% clearance of pleural opacities), or none (no response). The percentage of mean±standard deviation changes in the pleural opacity was −33.0%±9.9% in the UK group and −41.0%±14.9% in the alteplase group, respectively. On applying the Wilcoxon-Rank sum test, there was a significant difference in clearance of pleural opacities between the two drugs (p=0.014), which was statistically significant, favouring alteplase over UK (p=0.014) (Table 2).

2. Secondary objectives

1) Adverse side effects

Various side effects were also monitored and compared between the two study groups. The most reported side effects were fever and pain in the affected hemithorax. Pain was the commonest adverse side effect, occurring in 60% (n=18) of the patients in the UK group and in 40% (n=8) of the patients in the alteplase group. Chi-square test with Fisher's correction was applied. There was no significant difference in the secondary outcome in terms of fever (chi-square=0.292, p=0.740) and pain (chi-square=1.923, p=0.248) as adverse reactions between the two groups. The difference was not statistically significant (p=0.24) (Table 3).

Fever was the second most common side effect. The incidence of fever was 26.7% (n=8) in the UK group and 20% (n=4) in the group that received alteplase. However, similar to the side effect profile of pain, there was no significant statistical difference in the incidence of fever in the two study groups (p=0.74) (Table 3). Two patients developed severe adverse reactions in the alteplase group. They developed severe bleeding, and there was a drop in hemoglobin by more than 1 g%. The therapy was terminated after the first cycle. However, none of the patients required resuscitation or

component transfusion. There was no incidence of any severe adverse reaction in the UK group.

2) Association between the interval of symptoms to intervention with the response

There was also a statistically significant association between the interval of symptoms to intervention with the outcome of the IPFT. Patients who had reported within 6 weeks of symptoms were compared with those who reported relatively late, i.e., more than 6 weeks. More than 20% of X-ray clearance was taken as a cut-off for a significant response to IPFT. Further, 100% of patients (n=40) showed an excellent response to the therapy. In contrast, only 60% (n=6) of patients had a significant response in the group when they reported at more than 6 weeks after the onset of symptoms. Chi-square test with Fisher's correction was applied. There was a significant difference in the outcome when presentation was less than 6 weeks duration as compared to when it was more than 6 weeks of duration (chi-square) (Table 4).

Discussion

Tillet and Sherry[4] first demonstrated the use of fibrinolytic therapy in 1949 as a treatment for empyema. A group of 23 patients with loculated empyema or hemothorax received intrapleural instillation of STK and streptodornase through an intercostal drain. Several reports emerged thereafter, showing the effectiveness of fibrinolytic agents in the management of loculated pleural effusion[4]. However, the initial enthusiasm waned due to severe systemic side effects, such as fever and leucocytosis caused by various impurities in the enzyme mixture. The success rates of fibrinolytic agents still range from 38% to 100%[3,14,15].

The patients with CPE or empyema in whom antibiotic therapy and initial drainage fail are generally administered IPFT[10,11]. It is also a suitable option for patients who are not candidates for or do not want to undergo surgery. The rationale for this approach is that this strategy reduces the need for surgery and shortens the duration of hospitalization[3].

UK was effective in a randomized trial of patients with multiloculated pleural effusions[14,15]. Patients in the intervention group with UK showed significantly more drainage volume of pleural fluid, required less surgical referral, and required fewer days in the hospital. However, a randomized controlled trial (RCT) by Bouros et al.[17] in 1997 showed that UK had more fluid drainage after 24 hours than STK. The drainage volume in the first 24 hours was 380±99 mL in the STK group (p<0.001) and 420.8±110 mL in the UK group (p<0.001). but the total drainage volume at the end of the therapy was not statistically significant. The total volume of fluid drained after treatment was 1,596±68 mL in the STK group, and 1,510±55 mL in the UK group (p>0.05). An odds ratio (OR) of death or referral for surgery for STK versus UK was not significantly different (OR, 1.00; 95% confidence interval [CI], 0.13 to 7.72). A severe adverse reaction in terms of fever and an allergic reaction was significantly more frequent in the STK group. The author concluded that intrapleural STK or UK is an equally effective adjunct for managing CPE and it may reduce

Table 3. Showing adverse side effects of both the drugs

Variable	Fever	Pain
Total	46 (92.0)	4 (8.0)
Drugs	12 (24.0)	26 (52.0)
Urokinase	8 (26.7)	18 (60.0)
rt-PA	4 (20.0)	8 (40.0)
p-value	0.74	0.24

Values are presented as number (%).
rt-PA: recombinant tissue plasminogen activator.

Table 4. Showing comparison between radiological clearance between both the drugs

Variable	Clearance type		p-value
	Good clearance (>20% of the area on X-ray)	Poor clearance (<20% of area on X-ray)	
Early intervention (less than 6 weeks)	40 (100.0)	0	0.001
Late intervention (more than 6 weeks)	6 (60.0)	4 (40.0)	
Total	46 (92.0)	4 (8.0)	

Values are presented as number (%). Chi-square test with Fischer correction was applied. There was a significant difference in outcome between less than 6 weeks and more than 6 weeks of duration (chi-square).

the need for referral for surgery in some cases. Despite the comparable efficacy, UK could be the thrombolytic agent of choice due to the potentially dangerous allergic reactions to STK and a relatively little higher cost of UK[17].

Intrapleural rt-PA in patients with complicated parapneumonic pleural effusion and empyema has shown a significant response[18]. The landmark MIST2 study evaluated the efficacy of rt-PA, DNase, rt-PA plus DNase, and placebo in the treatment of CPEs[19]. Two hundred and ten patients were randomized to one of the above four regimens. The interventions were given twice daily for 3 days (rt-PA 10 mg, DNase 5 mg). The primary outcome measure was the absolute change in the pleural opacity on the chest radiograph from the day of randomization until 7 days post-randomization[19]. The administration of the combination of rt-PA and DNase resulted in a more significant reduction in the pleural opacity (–29.5%) than did the administration of rt-PA (–17.2%), DNase (–14.7%), or placebo (–17.2%)[19]. There were no significant differences between rt-PA, DNase, and placebo[19]. When the secondary endpoints were examined, the patients who received the combination showed a significant decrease in surgical referrals and a significantly shorter hospital stay than did the patients who received placebo[19]. rt-PA alone did not differ significantly from placebo in terms of either of these secondary endpoints, while DNase alone was associated with more surgical referrals than placebo[19].

Both UK and rt-PA have been used as IPFT agents and have proven efficacy against placebo, which has been shown in several previous trials[18-20]. However, data related to the comparative effectiveness of UK and alteplase are not abundant. Aleman et al.[15] conducted a double blinded RCT in 2015 and compared UK and alteplase's efficacy and adverse effect profile. A total of 99 patients were recruited, of whom 51 received alteplase and 48 received UK. Success rates for UK and alteplase at 3 and 6 days were not significantly different, but when only the subgroup of CPE was considered, UK resulted in a high proportion of cures. There were no differences in mortality or surgical need (overall, 3%). The OR of death comparing alteplase (combining 10 mg and 20 mg groups) with UK at 1 year was 0.94 (95% CI, 0.18 to 4.89)[21]. Five (28%) patients receiving 20 mg of alteplase and four (12%) patients receiving 10 mg presented with severe bleeding events. The author recommended that if intrapleural fibrinolytic agents are required, UK may be a more effective and safer agent than alteplase in patients with CPE[15].

Unlike the trial by Altmann et al.[21], our trial demonstrated that as compared to UK, newer fibrinolytic agents, such as alteplase, improved the drainage of infected pleural fluid and could lead to significant X-ray clearance (approximately 42% of the initial X-ray opacity compared to 33% in the UK group) (Table 2).

Bleeding was the most severe adverse effect noticed by Altmann et al.[21]. This study was at high risk of bias as several adverse events were identified in the 20 mg alteplase arm, which led to breaking of the blind after an interim analysis by the drug safety and monitoring committee. The protocol was altered, and the dose of alteplase was reduced to 10 mg daily[21].

Similar to the 2015 RCT, our trials also showed severe adverse reactions, such as bleeding, with the newer fibrinolytic agent, i.e., alteplase group, which was not observed in the patients treated with UK. Two of our patients in the alteplase group developed bleeding in the affected hemithorax after the initial dose of alteplase, which caused us to terminate the therapy after one cycle. However, alteplase was associated with comparable side effect profiles when common side effects were taken into consideration. The odds of fever (20.0% vs. 26.7%) and pain (40% vs. 60%) was low in the alteplase group, but this difference in the incidence was not statistically significant between the groups (Table 3). There was no incidence of life-threatening adverse reactions, such as severe bleeding and hypovolemic shock, requiring blood transfusion or severe anaphylactic reaction in any intervention group. This again highlights that both the drugs are safe when used as IPFT agents.

Our study also demonstrated that the early initiation of fibrinolytic therapy before the development of extensive pleural adhesion might lead to a favorable outcome and more pleural fluid drainage. A 5-year observational study from India reported that more than 75% of the non-responders presented at more than 6 weeks after initiation of symptoms[3]. On subgroup analysis, our study showed that 100% of the patients (n=40), who had received IPFT within 6 weeks of initiation of symptoms, had shown an excellent radiological clearance, compared to only 60% patients (n=6) among those who presented late, i.e., 6 weeks after initiation of symptoms. This difference was also statistically significant (p=0.001) (Table 4).

Our trial indicates that newer fibrinolytic agents, such as alteplase, may have greater efficacy than UK, as they improve pleural fluid drainage and produce significant radiological clearance. Alteplase has marginally fewer side effects than UK, but the difference is not statistically significant. However, unlike the UK group, a severe adverse reaction, such as bleeding, was seen in the alteplase group. Both the drugs have an excellent

safety profile, as none of them were associated with a life-threatening adverse reaction.

Our study has few limitations. One of the limitations of our study was the age group. The majority of the patients belonged to the young age group (between 20 and 30 years), which led to skewing of the age distribution graph to the right. However, this was an expected phenomenon as the majority of the clientele in our hospital are young individuals. We administered only a fixed number (two cycles) and dose of the drugs (UK 1,00,000 IU and alteplase 10 mg) to all the patients, irrespective of the extent and duration of the disease. Patients with extensive disease and those presenting late may require different doses and more cycles to show significant responses. Our study was a small single center trial, and further multicentric trials are necessary to determine the association of varying drug doses with the severity of the disease.

In conclusion, our trial showed that rt-PA (alteplase) has greater efficacy and it improves drainage and chest clearance when compared with UK. Although alteplase is associated with a higher incidence of bleeding, both the drugs were not associated with any life-threatening adverse event. Early initiation of fibrinolytic therapy before the development of severe loculation leads to better drainage and superior radiological clearance than in those who present late. From the previous studies and our trials, it may be concluded that IPFT is a safe and effective option for managing complicated pleural effusion or empyema, and newer agents, such as alteplase, have greater efficacy and a similar adverse effects effect profile when compared with conventional agents, such as UK.

Authors' Contributions

Conceptualization: Adhikari S, Marwah V, Choudhary R. Methodology: Adhikari S, Marwah V, Choudhary R, Pandey IM, Malik V, Pemmaraju A. Formal analysis: Adhikari S, Marwah V, Choudhary R. Data curation: Adhikari S, Marwah V, Choudhary R, Srinath V, Kapoor S. Software: Kapoor S. Validation: Adhikari S, Marwah V, Choudhary R, Kapoor S. Investigation: Adhikari S, Marwah V, Choudhary R, Pandey IM, Kumar TA, Malik V. Writing - original draft preparation: Adhikari S, Marwah V, Choudhary R. Writing - review and editing: Adhikari S, Marwah V, Choudhary R. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Funding

No funding to declare.

References

1. Malhotra P, Aggarwal AN, Agarwal R, Ray P, Gupta D, Jindal SK. Clinical characteristics and outcomes of empyema thoracis in 117 patients: a comparative analysis of tuberculous vs. non-tuberculous aetiologies. Respir Med 2007;101:423-30.
2. Kundu S, Mitra S, Mukherjee S, Das S. Adult thoracic empyema: a comparative analysis of tuberculous and non-tuberculous etiology in 75 patients. Lung India 2010;27:196-201.
3. Barthwal MS, Marwah V, Chopra M, Garg Y, Tyagi R, Kishore K, et al. A five-year study of intrapleural fibrinolytic therapy in loculated pleural collections. Indian J Chest Dis Allied Sci 2016;58:17-20.
4. Tillett WS, Sherry S. Streptococcal enzymatic debridement. Ann Surg 1950;131:12-22.
5. Bergh NP, Ekroth R, Larsson S, Nagy P. Intrapleural streptokinase in the treatment of haemothorax and empyema. Scand J Thorac Cardiovasc Surg 1977;11:265-8.
6. Diacon AH, Theron J, Schuurmans MM, Van de Wal BW, Bolliger CT. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. Am J Respir Crit Care Med 2004;170:49-53.
7. Simpson G, Roomes D, Heron M. Effects of streptokinase and deoxyribonuclease on viscosity of human surgical and empyema pus. Chest 2000;117:1728-33.
8. Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med 2006;174:817-23.
9. Light RW, Nguyen T, Mulligan ME, Sasse SA. The in vitro efficacy of varidase versus streptokinase or urokinase for liquefying thick purulent exudative material from loculated empyema. Lung 2000;178:13-8.
10. Ben-Or S, Feins RH, Veeramachaneni NK, Haithcock BE. Effectiveness and risks associated with intrapleural alteplase by means of tube thoracostomy. Ann Thorac Surg 2011;91:860-4.
11. Popowicz N, Bintcliffe O, De Fonseka D, Blyth KG, Smith NA, Piccolo F, et al. Dose de-escalation of intrapleural tissue plasminogen activator therapy for pleural infection: the Alteplase Dose Assessment for Pleural Infection Therapy project. Ann Am Thorac Soc 2017;14:929-36.
12. Vaudaux P, Waldvogel FA. Gentamicin inactivation in purulent exudates: role of cell lysis. J Infect Dis 1980;142:

586-93.
13. Colice GL, Curtis A, Deslauriers J, Heffner J, Light R, Littenberg B, et al. Medical and surgical treatment of parapneumonic effusions : an evidence-based guideline. Chest 2000;118:1158-71.
14. Nie W, Liu Y, Ye J, Shi L, Shao F, Ying K, et al. Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta-analysis of randomized control trials. Clin Respir J 2014;8:281-91.
15. Aleman C, Porcel JM, Alegre J, Ruiz E, Bielsa S, Andreu J, et al. Intrapleural fibrinolysis with urokinase versus alteplase in complicated parapneumonic pleural effusions and empyemas: a prospective randomized study. Lung 2015;193:993-1000.
16. Rahman NM, Maskell NA, Davies CW, Hedley EL, Nunn AJ, Gleeson FV, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest 2010;137:536-43.
17. Bouros D, Schiza S, Patsourakis G, Chalkiadakis G, Panagou P, Siafakas NM. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. Am J Respir Crit Care Med 1997;155:291-5.
18. Skeete DA, Rutherford EJ, Schlidt SA, Abrams JE, Parker LA, Rich PB. Intrapleural tissue plasminogen activator for complicated pleural effusions. J Trauma 2004;57:1178-83.
19. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med 2011;365:518-26.
20. Idell S. Update on the use of fibrinolysins in pleural disease. Clin Pulm Med 2005;12:184-90.
21. Altmann ES, Crossingham I, Wilson S, Davies HR. Intra-pleural fibrinolytic therapy versus placebo, or a different fibrinolytic agent, in the treatment of adult parapneumonic effusions and empyema. Cochrane Database Syst Rev 2019;2019:CD002312.