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Review Article

To lyse or not to lyse? Use of intrapleural tissue plasminogen activator and DNase in the management of parapneumonic effusions and empyema

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ABSTRACT

Despite a range of management options, pleural effusions and empyema continue to present therapeutic challenges in the clinical setting. With treatment options ranging from simple use of antibiotics to more complex surgical procedures, several important considerations need be made as to what type of treatment is best for each patient on a case by case basis. One treatment modality of increasing interest is the use of intrapleural fibrinolytics to facilitate drainage of effusions. This presents a viable option especially in patients in whom surgery is not preferred. But, as with many therapeutic approaches, the use of intrapleural fibrinolytics is laden with significant controversies and has been a subject of considerable debate over the last couple of years. With accruing evidence for and against this modality of treatment, the ensuing discussion has been whether or not it should be a routine treatment choice and which group of patients should this consideration be made for. This paper gives a background on the epidemiology and etiology of parapneumonic effusions and empyema and briefly outlines the available options of management. Furthermore, we extensively discuss available evidence on the use of intrapleural fibrinolytics as a management option for parapneumonic effusions and empyema, with particular emphasis on use of tissue plasminogen activator and DNase.

Keywords: DNase, Empyema, Intrapleural fibrinolytics, Parapneumonic effusion, Tissue plasminogen activator

INTRODUCTION

Parapneumonic effusions and empyema remain significant clinical issues and continue to present a huge burden of care, with documented increase in incidence and only marginal improvement in clinical outcomes for decades.[1] Parapneumonic effusion (PPE) is generally defined as fluid accumulation in the pleural space secondary to (a viral or bacterial) pneumonia or due to a lung abscess. It may progress to become empyema which, simply put, refers to collection of pus in the pleural space.[2] Empyema may sometimes result primarily without any parenchymal infection. PPE and empyema constitute a significant burden with current estimates putting annual adult incidence in the United States and United Kingdom at greater than 80,000 cases.[3] There have been reports of unexplained increase in incidence of pleural infections, PPE and empyema in the last couple of decades. A statewide retrospective study by Farjah et al which included 4,424 patients who were hospitalized for pleural infections and underwent some form of drainage between 1987 and 2004 showed a yearly increase of 2.4% in incidence.[4] Grijalva et al also collected data over a 13-year period from a large nationwide inpatient sample database and found a 2-fold increase in the rate of parapneumonic empyema hospitalizations in the United States from 3.04/100000 in 1996 to 5.98/100000 in 2008. Their data also showed some variation with age with the

largest rate of increase observed in people aged 40-64 years.[1]

Clinical outcome also seems to have worsened or at best remained stagnant in spite of advances in medical care over the decades. One study showed a 1.8-fold increase in rate of fatal hospitalizations, another found that parapneumonic empyema deaths were about six-times more between 2000-2004 compared to 1975-1980 in Utah.[1,5] Parapneumonic effusions complicate about 20-40% of pneumonia cases and worsen prognosis with some studies demonstrating the presence of pleural effusion as an independent predictor of short-term mortality and one study showing up to a 6.5-fold increase in mortality in pneumonia complicated by bilateral effusion.[2,6,7]

PATHOPHYSIOLOGY AND CLASSIFICATION

Over half a century ago, the American Thoracic Society (ATS) put forward a description of parapneumonic effusions that attempts to elucidate the pathophysiologic process of the clinical condition in three stages best seen as a continuum.[8]

The first stage features accumulation of fluid in the pleural cavity derived largely from the movement of pulmonary interstitial fluid into the space but also from extravasation of fluid due to increased vascular permeability both owing to the ongoing inflammatory process in the lung. This stage, known as the exudative stage is characterized by pleural fluid glucose levels greater than 60 mg/dl, a high pH greater than 7.2, low lactate dehydrogenase (LDH) levels with no evidence of bacterial infection on gram staining or culture. If unattended or wrongly attended to, the process continues and now involves bacterial invasion with accompanying cellular inflammation and activation of the coagulation cascade leading to positive bacterial studies, a more acidic pH less than 7.2, glucose levels less than 60 mg/dl, and high LDH levels in the pleural fluid. This stage is also characterized by fibrin deposition and septations within the pleural cavity and is thus known as the fibrinopurulent stage. In the third stage, the effusion becomes organized and fibroblasts invade the pleura, forming a thick pleural peel which prevents adequate expansion of the lung. Some authors have referred to the exudative stage as simple PPE and the fibrinopurulent and organized stages as complicated PPE.[2]

Following this initial classification by the ATS, several other classification schemes ensued. In 1980, a publication in the American Journal of Medicine described a system that classified the clinical spectrum into simple PPE, complicated PPE, or empyema.[9] 15 years later, light will describe a more complex classification into seven groups with a focus on treatment options. He proposed that classes 1 to 3 require no more than antibiotics with or without thoracocentesis, classes 4 and 5 require tube thoracostomy drainage with possibility of surgical decortication as the condition worsens to classes 6 or 7.[10]

In 2000, the American College of Chest Physicians (ACCP) adopted a risk stratification approach which categorized patients into four levels with increasing risk of poor outcome based on a combination of three parameters namely pleural space anatomy, bacteriology and chemistry.[11] More recently, the British Thoracic Society (BTS) proposed a simple model of classification similar to the that described by Light et al. Important parameters in classification were noted to be pleural fluid appearance, pH, LDH and glucose levels, as well as presence of organisms on gram staining or culture.[12]

The bacteriology of PPE and empyema features both aerobic and anaerobic organisms with a predominance of aerobic organisms and with some variations hinged on whether it is community- or hospital-acquired pneumonia. Worthy of note is that in many cases, it is difficult to isolate a pathogenic agent. Commonly isolated aerobes include *Staphylococcus aureus*, *Streptococcus pneumonia*, *Escherichia coli*, *Haemophilus influenza*, *Klebsiella Pneumoniae*. Some of the anaerobes implicated include *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Provetella spp*.[13,14]

MANAGEMENT OPTIONS FOR PARAPNEUMONIC EFFUSIONS AND EMPYEMA

Despite being a disease that has been present for ages, having been described as far back as the time of Hippocrates about 2500 years ago, there is still great variation in the management of parapneumonic effusions and empyema with a wide range of possible treatment options.

The treatment modalities can be either non-operative or operative. Non-operative treatments include use of antibiotics, chest tube drainage or intrapleural fibrinolysis. Surgical approaches include thoracoplasty, thoracotomy and decortication, video assisted thoracoscopic surgery (VATS), and debridement or open thoracostomy drainage in debilitated patients.[2,15] Principal concerns in patient care remain appropriate patient selection and timing for the best possible outcome as several factors confound selection, including the stage of the disease, age of the patient, presence of comorbidities, fitness or willingness of patient for surgery, amongst others.

INTRAPLEURAL FIBINOLYTICS IN THE MANAGEMENT OF PARAPNEUMONIC EFFUSIONS AND EMPYEMA

The "first-generation" fibrinolytics

The earliest description of the use of intrapleural fibrinolytics in the literature was in 1949 when Tillet and Sherry documented increased pleural fluid drainage with

intrapleural administration of partially purified concentrates of streptokinase and deoxyribose nuclease in their study of 23 patients with exudative pleurisy.[16] 70 years later, however, the use of these agents is still a subject of considerable debate.[3] After about three decades of silence on the topic, there came a series of initial, uncontrolled studies on the efficacy and safety of intrapleural fibrinolytics (Table 1).

Table 1: Initial uncontrolled studies on use of intrapleural fibrinolytics.

Study	Year	Subjects	Fibrinolytic	End points	Findings
Bergh et al[17]	1977	38	Streptokinase	Increase fluid drainage Lung re-expansion	79% success
Moulton et al[18]	1989	13	Urokinase	Complete drainage of pleural fluid	92% success
Temes et al[19]	1996	26	Streptokinase or urokinase	Complete resolution of symptoms CXR improvement No surgery or empyema tubes	69% success
Laisaar et al[20]	1996	28	Streptokinase	Resolution of pleural collection No further need for surgery	72% success
Jerjes et al[22]	1996	48	Streptokinase	Resolution of pleural collection Radiologic and spirometric improvement	92% success
Bouros et al[25]	1997	50	-25 Streptokinase -25 Urokinase	Clinical and radiologic improvement	Similar positive outcomes >adverse events with SK >cost with UK

SK- Streptokinase; UK- Urokinase

Table 2: Controlled studies on the use of intrapleural fibrinolytics.

Study	Year	Participants	Methods	End points	Findings
Chin et al[23]	1997	52 -29 drain only -23 drain + SK	Not randomized Not blinded	Volume of fluid drained Duration of hospital stay Need for surgery Mortality	-Increased drainage with SK -No significant difference in morbidity and mortality
Davies et al[24]	1997	24 -12 SK -12 Saline	Randomized	Volume of fluid drained Radiological response	-Significantly increased drainage and improved CXR with SK (surgery required in 3 controls, but none in SK)
Bouros et al[25]	1999	31 -15 UK -16 Saline	Randomized Double-blinded	Fluid drainage Radiographic improvement	- Complete drainage in 86.5% vs. 25% (when remaining 12 got UK, complete drainage was seen in 50% of them)
Tuncozgur et al[26]	2001	49 -UK -Saline	Randomized	Time to defervescence Need for decortication Duration of hospitalization	- Shorter with SK - Lower with SK - Shorter with SK
Diacon et al[27]	2004	44 -22 SK -22 Saline	Randomized Double-blinded	Clinical success Need for surgery	No difference in 3 days, significant increase at day 7
Maskell et al[14]	2005	427 -206 SK -221 Placebo	Randomized Double-blinded Multicenter	1^0 – Death or surgery at 3 months 2^0 – Rates of death or surgery, radiographic improvement, length of hospital stay	No significant difference in 1^0 outcome (SK 31% vs Placebo 27%, RR:1.14, p=0.43) nor with 2^0 outcomes > Adverse events with SK

SK- Streptokinase; UK- Urokinase; CXR- Chest X-ray

Bergh et al, in 1977, administered intrapleural instillations of streptokinase to 38 patients with empyema or hemothorax and noted increased fluid drainage in all cases without any serious complications.[17]

A similar study of 13 patients was conducted more than a decade later, this time using urokinase as the fibrinolytic agent. The study recorded complete fluid drainage in 92% of the participants.[18] In 1996, three other studies were published with similar results.[19-21] Attempts at comparing both agents led to the only head-to-head double-blinded study comparing streptokinase with urokinase which showed similar positive outcomes with both of them but noted higher adverse effects with streptokinase and slightly higher cost with urokinase.[22] Although, these studies all showed a potential benefit, they were small and not methodologically strong enough to guide decision making.

These initial studies were followed by controlled studies with better designs (Table 2). The first was a 5-year study of 52 patients with PPE and empyema.[23] Their study was neither randomized nor double-blinded but simply recruited consecutively into the drain only arm for the first half of the study and into the drain plus intrapleural streptokinase arm in the remaining half. They found that although there was significantly increased fluid drainage with the addition of streptokinase, it made no significant difference on overall morbidity and mortality.[23] Davies and colleagues randomly assigned 24 patients to receive either streptokinase treatment or saline infusion as control and observed significantly more fluid drainage and better radiological response in patients treated with streptokinase. Surgical therapy was necessary in three patients in the control group but in no patient in the treatment group.[24]

Notably, the two studies discussed above used streptokinase as the fibrinolytic agent, but in 1999, a randomized, double-blinded trial of urokinase versus placebo showed similar results. Complete fluid drainage was recorded in 86.5% of patients in the urokinase group and in only 25% of patients in the control group. When the remaining patients in the control group were subsequently treated with urokinase, 50% of them had complete drainage.[25]

Another group randomly assigned 49 patients to receive either intrapleural urokinase or saline. They found shorter duration to defervescence (7±3 vs.13±5 days, $p<0.01$), greater volume of fluid drainage (1.8±1.5 vs. 0.8±0.8 liters, $p<0.001$), lower rate of decortication (29.1% vs. 60%, $p<0.001$), and shorter length of hospital stay (14±4 vs. 21±4 days, $p<0.001$) in the patients treated with urokinase.[26] Diacon et al. conducted a single-center, controlled trial randomizing patients to treatment with either intrapleural streptokinase or placebo. After 3 days, they recorded no difference between both groups. However, at the end of 7 days of treatment, the streptokinase arm recorded higher clinical success rates (82% vs. 48%, p=0.01) and lower rates of surgical referral (45% vs. 9%, p=0.02). Furthermore, when they followed up for over 6 months, they observed no significant differences in radiologic and functional status of patients in both arms.[27]

Thus, despite accruing evidence on the use of intrapleural fibrinolytics in the treatment of PPE and empyema, there were still significant concerns with the true efficacy. A closer look at the studies discussed above may reveal some methodological weaknesses. First, the studies were rather small and there was significant heterogeneity in the study samples. Moreover, only two of the studies were double-blinded.[25,27] There is also the high likelihood of publication bias, in which case, studies that fail to find significant positive results remained unpublished.

These concerns were apparently reinforced when, in 2005, a large study with a robust design to test the use of intrapleural fibrinolytics in complicated pleural effusions was published.[14] The MIST 1 study was a U.K. multicenter, double-blinded randomization of 427 patients to receive either streptokinase or placebo via intrapleural instillation. The study found no significant difference between the groups in the primary outcomes of number of deaths or need for surgical treatment (streptokinase 31%, placebo 27%, relative risk 1.14 (95% confidence interval: 0.85-1.54) p.0.43). Furthermore, when the secondary outcomes such as rates of death, surgery rates, length of hospitalization and radiographic improvement, there was still no demonstrable benefit of streptokinase use. In fact, the study reported more serious adverse events in the streptokinase group (7% vs 3%, relative risk 2.49 (95% confidence interval 0.85-1.54), p.0.08).[14]

A 2008 Cochrane collaboration review attempted to put everything together. The authors concluded that although there appears to be an overall potential benefit, results had to be treated with caution. They identified issues such as heterogenous data, low quality trials and too wide confidence interval that made it difficult to exclude possibility of adverse effects.[28] It was obvious that better designed studies were needed and the possibility of alternative agents needed to be explored.

EVIDENCE FOR TISSUE PLASMINOGEN ACTIVATOR AND DNASE USE

The results of the MIST 1 trial may have led to a re-evaluation of the fibrinolytic agents used in the management of complicated pleural effusions. The rationale for the use of fibrinolytics is the understanding that fibrin is deposited in the fibrinolytic stage of the disease, as described above, leading to loculations/ septations which make drainage difficult. Minimum levels of plasminogen in the pleural fluid are required for adequate fibrinolytic effect of streptokinase but evidence shows that plasminogen levels are very low in pleural effusion.[29] On the other hand, tissue plasminogen

activator (tPA) action appears to be independent of plasminogen levels, and initial small, uncontrolled studies have reported positive results with the use of tPA alone for management of PPEs.[30,31] Later in 2012, a double-blinded cross-over trial comparing alteplase (tPA) with placebo in patients with empyema or complicated PPE was published. 58 of 61 patients had resolution of pleural collection with alteplase while 4 of 32 patients had resolution with placebo ($p<0.001$).[32]

The viscosity of pus is also an important factor in pleural fluid drainage and is thought to be related to deoxyribonucleoprotein levels caused by degradation of leucocytes. Theoretically, intrapleural DNase should thus have an effect in reducing this viscosity. In fact, in-vitro studies have already demonstrated this and also showed superiority of DNase over streptokinase/urokinase in thinning pus.[33]

This understanding of the shortfalls of streptokinase use, as well as the attractive potential benefit of combining tPA with DNase likely led to the MIST 2 trial. It was a 2-by-2 factorial, randomized, double-blinded, double-placebo multicenter study with 4 arms; tPA only, DNase only, tPA-DNase combination, and placebo. The primary end point of the study was change in pleural opacity on chest radiograph at Day 7, while the secondary outcomes were surgical referral, length of hospitalization and adverse effects. The study found that change in pleural opacity was significantly higher in the combination tPA-DNase arm than in the placebo arm (-29.5±23.3% vs. -17.2±19.6%, 95% confidence interval -13.4 to -2.4, $p=0.005$) but this difference was not seen in the single agent groups and the placebo group. The frequency of surgical referral and the length of hospital stay were both lower in the combined tPA-DNase group while there was no significant difference in adverse events among all four groups.[34] The results of this large and robustly designed study stimulated interest and clinical use of the combination, but there remain yet unanswered important questions such as the definite treatment effects, appropriate dosing regimen and timing of use, amongst others.

In 2014, Piccolo and colleagues provided evidence again in support of tPA-DNase use in their multinational observational study involving 107 patients with 92.3% of the patients being successfully managed with tPA-DNase without need for further surgical treatment.[35] This study used similar dosing protocol as the MIST 2 trial but 84% of the patients received tPA-DNase only after initial conservative treatment had failed as opposed to immediately post-randomization in the MIST 2 trial, yet the results were satisfactory. This result showed that tPA-DNase may have a role as “rescue therapy” in cases of failed initial treatment with antibiotics and tube drainage.

Appropriate dosing and administration are other important questions on the use of these agents. The MIST 2 trial used serial administration of each of the agents at 5mg of DNase and 10mg of tPA. However, this protocol appears cumbersome and may constitute significant burden to health personnel. A retrospective observational study of 39 patients in a facility showed that co-administration of both agents twice daily for 3 days was also effective (85% treatment success without need for surgical treatment) and safe (only one case of complication).[36] Another retrospective study of 55 patients had a 92.7% success rate while utilizing a once-daily regimen.[37] There have also been reported cases of success with combined intrapleural therapy containing lower doses of tPA than that used in the MIST 2 trial; 5mg tPA + 5mg DNase, and as low as 1mg tPA + 5mg DNase.[38,39] Ultimately, the establishment of a relatively low effective dose could potentially further decrease the risk of adverse reactions. Recently, an ex-vivo pleural fluid test, the fibrinolytic potential, is being developed with the aim of enabling personalized dosing regimen for individual patients rather than flat dosing currently in use.[40]

In light of the above evidence, tPA and DNase are potentially of clinical benefit in the management of complicated PPE but more studies are required to determine whether these agents are suitable for routine use and what the appropriate dosing protocol should be.

CONCLUSION

Despite the long-standing debate on use of intrapleural fibrinolytics, there is evidence supporting the clinical benefit of the use of tPA and DNase in the treatment of parapneumonic effusion and empyema. Important questions remain whether or not they should be routinely administered, what the appropriate dosing regimen should be, and concerns about severe adverse effects.

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