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An international survey on the use of intrapleural tissue plasminogen activator/DNase therapy for pleural infection

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Shareable abstract (@ERSpublications)
This international survey observed a large variation in the delivery of tPA/DNase therapy for pleural infection. Respondents were open to the concept of starting with a lower (<10 mg) dose of tPA (with the possibility of escalation) if evidence accumulates. https://bit.ly/2ZfPRrL

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Abstract

Introduction Intrapleural tissue plasminogen activator (tPA) combined with human recombinant DNase (DNase) could be an effective alternative to surgery in managing pleural infection, as demonstrated in the Multi-centre Intrapleural Sepsis Trial (MIST)-2. However, the optimal delivery regimen is still unknown. The aim of this survey was to identify the current practice of tPA/DNase use by physicians with published interests in pleural infection, and their opinions on dose de-escalation of tPA/DNase therapy.

Methods Potential participants were identified using four search strategies. Only practising physicians who were managing patients with pleural infections and either actively involved in pleural research and publications, or were members of relevant pleural disease guideline panels at the time of survey were included.

Results An invitation email with the questionnaire was sent to 102 participants, of whom 49 (48%) responded. Most respondents (90%, n=44) have used tPA/DNase to manage pleural infection, but the dosing and delivery regimens employed varied. Many (86%, 38 out of 44) respondents have used 10 mg tPA, while 73% (n=32), 16% (n=7) and 9% (n=4) have used 5 mg, 2.5 mg and 1 mg doses, respectively. Most respondents instilled tPA/DNase concurrently (61%, n=27) and routinely administered six doses of tPA/DNase (52%, n=23) twice daily (82%, n=36). Respondents would consider using a lower starting dose of tPA (with the possibility of escalation if clinically needed) if a median 80% (interquartile range 50–80%) of patients could be successfully treated at that dose.

Conclusion This survey observed a large variation in the current treatment protocol of intrapleural tPA/DNase therapy worldwide and the need for more data on this subject.

Introduction

Pleural infection accounts for >90 000 hospital admissions in the United States alone each year [1]. It is associated with high morbidity and a mortality of 25% in the elderly [2]. Despite being a centuries-old illness, the incidence of pleural infection continues to rise, causing a significant healthcare burden [3, 4]. In recent years, several observational studies and randomised clinical trials have focused on exploring the effectiveness of intrapleural fibrinolytic therapy in the management of pleural infection as an alternative to surgery [2, 5, 6].

Fibrinolytics, such as tissue plasminogen activator (tPA), break down fibrinous loculations within the pleural space, while human recombinant DNase (DNase) reduces pleural fluid viscosity, allowing a more effective evacuation of infected pleural fluid [5]. Findings from the Multi-centre Intrapleural Sepsis Trial

(MIST)-2 demonstrated that combined tPA/DNase therapy in the management of pleural infection enhanced pleural drainage and reduced the need for surgery and length of hospitalisation [6]. This remarkable breakthrough has generated significant interest worldwide, but the adoption of tPA/DNase therapy into treatment has been variable.

Since the publication of MIST-2, several studies attempted to optimise intrapleural tPA/DNase therapy, focusing particularly on two hurdles of implementation: the complexity of the intrapleural instillations and clinicians' concerns of the costs and risks of tPA. First, the original delivery protocol in MIST-2 involved instillation of tPA, followed by clamping of the chest tube which was then reopened for drainage before DNase was instilled following the same steps [6]. The process was delivered twice a day for six doses. This regimen demands considerable staff time, and in some centres only clinicians (not nurses) are allowed to perform these intrapleural instillations, creating significant time pressure. Various studies have piloted different simplified delivery methods, all aimed to reduce demand on complexity of the delivery regimen [1, 7, 8]. Second, tPA is expensive and is associated with potential bleeding risks. The original dose of 10 mg was chosen empirically without a phase I dose-escalation assessment. Studies testing efficacy of lower tPA doses have reported promising results [7, 9], but no head-on randomised trials have been performed to evaluate these lower dosing regimens.

The lack of data on optimal tPA/DNase doses, administration protocols and cost-effectiveness are likely to create heterogeneity in practice. The objective of this study was to survey international pleural experts on current tPA/DNase treatment protocols used in clinical practice and to seek their opinion on acceptable treatment success rates with dose de-escalation in the management of pleural infection. This will provide insight into the current adoption of tPA/DNase therapy and the concerns limiting its use, providing guidance on future directions into intrapleural tPA/DNase research.

Methods

We conducted a descriptive, cross-sectional, international survey to identify the use of tPA/DNase in practice by physicians with published interests in pleural infection, and their opinions on dose de-escalation of tPA/DNase therapy. The targeted participants were practising physicians who were managing patients with pleural infections and either actively involved in pleural research and publications (recognised as first and last authors), or members of pleural disease guideline groups/committees.

To identify potential survey participants meeting these criteria, four literature search strategies were performed. Articles were selected after a structured literature review carried out between March and May 2019. Key terms employed were "intrapleural" or "pleural infection" or "empyema" or "parapneumonic" or "pleural effusion" or "pleural empyema" OR "tPA" or "alteplase" or "tissue plasminogen activator" or "fibrinolytic" OR "DNase" or "deoxyribonuclease" or "dornase alpha".

Search was limited to publications on human studies of adults aged >18 years published since 2009. Authors of published articles citing MIST-2 (n=260) as well as authors cited within the current (2010) British Thoracic Society pleural disease guidelines, including its medical members, were also identified. Duplicates were removed and participants were included in the mailout if they were identified as current practising physicians with identifiable contact information at the time of search.

A questionnaire, containing 18 questions (supplementary table S1) was developed using Qualtrics software (Provo, UT, USA; September 2019), and was reviewed for content validity by five local clinicians with pleural interests at Sir Charles Gairdner Hospital (Perth, Australia). Ethics approval was granted by the human research ethics committee of the University of Western Australia (RA/4/20/5593).

An initial email invitation was sent to all participants. Each participant was provided with a unique link to ensure a single submission per participant over a 4-week period. A follow-up email was sent to nonrespondents after a 2-week period. Questionnaire responses were de-identified. Data were analysed using GraphPad Prism 9.1.0 (La Jolla, CA, USA) and were presented as median (interquartile range (IQR)). Results were considered significant at $p<0.05$.

Results

119 physicians were identified using the search strategies described. After screening for contact information, 17 physicians were excluded: 16 had no identifiable contact information, and one was deceased. The remaining 102 physicians were sent an invitation email for participation. Out of the 102 physicians contacted, 49 (48%) completed the survey. These physicians estimated that they had treated a combined total of 1342 (median 20) patients with pleural infections in the past 12 months. They were

based in Europe (n=22), USA (n=14), Australia (n=6), New Zealand (n=3), Asia (n=2) and one each from Africa and Canada. Of these physicians, 28 identified their primary area/speciality as respiratory/pulmonary medicine (57%), 18 as interventional pulmonology/pleural speciality (37%) and three as thoracic surgery (6%).

Variations exist in the current treatment protocols of intrapleural tPA/DNase therapy used by the respondents (table 1). Most respondents (90%, n=44) have used tPA/DNase for the management of pleural infections in their patients. The remaining 10% did not adopt tPA/DNase therapy in their practice due to either insufficient data on safety and efficacy (n=1), therapy not approved for used/available in their current workplace (n=2) or surgery being the preferred option (n=2). The analyses presented herein are on the 44 respondents who have used tPA/DNase in their practice.

Of those who have used tPA/DNase to manage pleural infections, 20% (eight from USA and one from Australia) used tPA/DNase routinely in all patients admitted with pleural infections under their care. The remainder (n=35) estimated that they used tPA/DNase in a median 50% (IQR 30–70%) of their patients. When asked about the reason for not using tPA/DNase routinely in all patients (respondents were allowed to select more than one reason), most of them (70%, n=31) selected the option of "I only use tPA/DNase in patients who failed to respond to conventional treatment (antibiotics and chest tube drainage)". Other reasons selected include insufficient efficacy (n=6) or safety (n=2) data, only using tPA/DNase as a last-line treatment prior to surgical referral (n=6) and prohibitive cost (n=4). Some respondents provided additional comments stating they would decide treatment on a case-by-case basis depending on the pleural space appearances on ultrasound and computed tomography scans (n=1), reserve tPA/DNase therapy for patients not suitable for surgery (n=2), when surgery might be delayed (n=1) or as an attempt to avoid surgery (n=1). One respondent declared the use of urokinase instead of tPA due to personal perceived efficiency and cost effectiveness (n=1).

tPA doses

The respondents used a range of tPA doses (10 mg, 5 mg, 4 mg, 2.5 mg and 1 mg), with the higher doses (10 mg and 5 mg) more commonly employed than the lower ones (2.5 mg and 1 mg) (figure 1). In addition, 27% (n=12) and 11% (n=5) of respondents have only used 10 mg and 5 mg tPA, respectively. When asked what the respondents perceived was the lowest effective dose, 70% (19 out of 27) chose 5 mg tPA, while others believed that 10 mg (n=3), 2.5 mg (n=3), 2 mg (n=1) and 1 mg (n=1) were the lowest effective tPA doses. The rest (n=17) of the physicians did not specify a dose.

tPA/DNase administration and dosing regimen

Most respondents (61%, n=27) delivered tPA/DNase concurrently into the pleural space using two separate syringes (*i.e.* drugs not admixed before instillation), while others adhered to the MIST-2 protocol by administering them separately. One respondent reported to have administered tPA/DNase concurrently in

TABLE 1 Summary of survey results

Physicians using tPA/DNase	44/49 (90)
Physicians using tPA/DNase in all patients	9/44 (20)
Doses of tPA used[#]	
10 mg	38 (86)
5 mg	32 (73)
4 mg	1 (2)
2.5 mg	7 (16)
1 mg	4 (9)
tPA/DNase administration[#]	
Concurrently	27 (61)
Separately	15 (34)
Number of tPA/DNase doses[#]	
<6 doses	20 (45)
6 doses	23 (52)
Dosing frequency[#]	
Once daily	8 (18)
Twice daily	36 (82)

Data are presented as n/N (%). tPA: tissue plasminogen activator; DNase: human recombinant DNase. [#]: n=44 physicians.

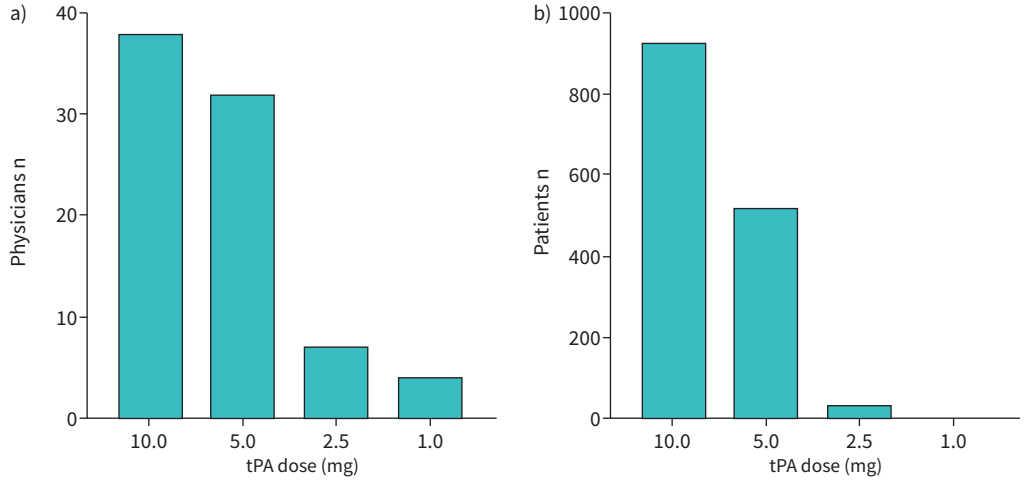

FIGURE 1 a) The total number of physicians using 10 mg, 5 mg, 2.5 mg and 1 mg of tissue plasminogen activator (tPA); b) the estimated total number of patients given the respective tPA doses (plotted based on data from physicians who responded to the question).

one syringe. Another administered the initial dose of tPA and DNase separately, but the subsequent doses concurrently.

More than half the respondents (52%, n=23) used six doses of tPA/DNase in each patient as per the MIST-2 protocol, while the remaining respondents may use fewer than six doses per patient, based on clinical response. Most respondents (82%, n=36) adopted a twice-daily dosing regimen, whereas only 18% of them used it once daily. Ward limitations and the complexity of the pleural space have also determined the dosing regimen for two respondents.

Although 27% (n=12) of respondents reported that they would not deviate from their usual protocol under any circumstances, 73% (n=32) of them would, based on various reasons, including patient's bleeding risk and clinical response, complexity of the infection, side-effects, staffing issues and costs. One respondent reported to have used a simplified regimen (not specified) to enable administration by junior staff in a nonrespiratory inpatient service.

Dose de-escalation

There are ongoing dose de-escalation studies to establish the lowest effective tPA dose. It is anticipated that with decreasing dose of tPA, the number of successfully treated patients will also decrease. As such, physicians were asked for their acceptable "minimum percentage of patients successfully treated at a lower dose for dose de-escalation to be considered successful". Our question specifically stated that the dose of tPA could be raised if clinical response was inadequate. Respondents considered it a success if a median 80% (IQR 50–80%) of patients were successfully treated with a certain starting dose of tPA. However, they would only adopt lower doses of tPA in their protocol if ⩾100 (IQR 50–200) patients have been successfully treated in published (*e.g.* retrospective observational) studies. Some respondents also commented on the need for more evidence-based trials in this area.

Discussion

This study is the first to provide insight on the real-world use of intrapleural tPA/DNase therapy in clinical practice. Although most clinicians surveyed have used tPA/DNase therapy, there is a large variation in dosage regimen and administration protocols between physicians around the world.

As the treatment regimen in MIST-2 protocol is labour-intensive and time-consuming, it is not surprising that practice has evolved into many different variations in order to be adapted to local conditions. In addition, recent findings on concurrent administration of tPA/DNase and the efficacy of 5 mg tPA from our observational studies may have influenced the physicians' decisions [8, 9]. Replies of the respondents suggest that physicians require more safety and efficacy data before they would consider dose de-escalation in their practice. Hence, there is clearly a need for more controlled studies in order to determine the best possible outcome.

More recently, a consensus statement by an international group of 22 experts was published to address the knowledge gap on the use of tPA and DNase in adult patients with pleural infection [10]. The consensus-based recommendations provide a standardised guidance since the publication of MIST-2 trial, which will be valuable considering the wide variation in treatment protocols worldwide at present, as shown in the survey results.

This study has limitations. First, we limited the survey to clinicians with published interests in tPA/DNase and/or pleural infection. This selected population is no doubt likely to include the strongest advocates of the use of tPA/DNase and cannot be considered representative of the general clinician population. The confidence and experience needed to aid the decision-making process may also be lacking in other physicians. Second, to keep the survey simple, we did not further categorise pleural infections (*e.g.* community- or hospital-acquired or indwelling pleural catheter-related infections), which may alter the replies. Third, like any survey, the answers were based on physicians' perceived views and recall of personal experiences and cannot be interpreted as necessarily evidence based. Fourth, it is almost certain that clinicians may individualise treatment to particular patients (*e.g.* lower doses for older patients with higher bleeding comorbidities), which is beyond the scope of this survey.

In conclusion, this survey shows that there is a need for further investigations on the practical aspects of intrapleural tPA/DNase therapy in the management of pleural infection given the uncertainties about the best delivery regimens. The study highlighted implementation challenges, especially the complex, labour-intensive MIST-2 protocol. In addition, it is worth noting that this is a constantly evolving field and the "one size fits all" approach may not be suitable as we work towards personalised treatment. Future studies should aim at investigating the lowest effective dose and comparing the safety and efficacy of different treatment regimens and administration protocols of intrapleural tPA/DNase. Further investigations into subgroups of pleural infection and high-risk populations will be useful.

Provenance: Submitted article, peer reviewed.

Ethical approval: This study was approved by the human research ethics committee of the University of Western Australia (RA/4/20/5593).

Conflict of interest: E.P.M. Lau has nothing to disclose. M. Eshraghi has nothing to disclose. K. Dootson has nothing to disclose. C. Yeoh has nothing to disclose. W. Ywe Phu has nothing to disclose. Y.C.G. Lee is an honorary consultant to Lung Therapeutics Ltd. N.D. Popowicz has nothing to disclose.

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