Intrapleural fibrinolytics for the treatment of thoracic empyema: Analyzing differences in treatment options at Oregon Health & Science University hospital

Abstract

Background

The incidence of pleural infections in the United States has grown over the last 30 years (Shen et al., 2017). With a mortality rate between 10% and 20%, it is imperative that these patients are treated quickly and effectively (Rahman et al., 2011). The goal of treatment is to drain infected fluid from the pleural space, which can be accomplished through the placement of a chest tube and fibrinolytics. Currently, there is little consensus on which fibrinolytic to use and what doses are needed for optimal treatment of thoracic empyemas, which is the presence of pus in the pleural cavity (Davies et al., 2010). This has led to a lack of standardized care among providers and institutions (Idell & Rahman, 2018). The goal of this project was to determine if the use of intrapleural tPA and Dornase (DNase) is more effective than intrapleural tPA alone in treat patients with empyemas at Oregon Health & Science University (OHSU) hospital.

Methods

Data was retrospectively collected from patients' charts that were treated for thoracic empyema using chest tube drainage between January 2018 and December 2018 at Oregon Health & Science University hospital. Data points included basic demographic data (age and sex), number of days a chest tube was in place, the type of fibrinolytic used, the dose of each fibrinolytic used, and the frequency each fibrinolytic was given. End points that were evaluated included length of stay, resolution of the infection, and whether or not the patient required surgical

intervention to clear the infected fluid. The Mann-Whitney U test was then used to determine if there is a statistically significant difference between the two treatment groups. No interventions were performed as this was a retrospective data analysis.

Results

This small project enrolled 16 participants (10 males, 6 females) over the age of 18 (average age 64.4 $\pm$ 13.1) who were treated for thoracic empyema at OHSU hospital. All sixteen patients experienced a resolution of infection and none required surgical intervention. The median length of stay for the tPA cohort was 16.5 $\pm$ 13.9 days compared to 13.5 $\pm$ 3.3 days for the tPA-DNase group (p=0.45). The tPA-DNase cohort had a median of 6.5 $\pm$ 3.4 days with a chest tube in place versus 8.5 $\pm$ 12.3 days in the tPA only group (p=0.26). Similarly, there was no statistically significant evidence of a difference between the groups in number of doses required (tPA avg.= 3.08, tPA-DNase avg.= 2.75, p=0.95).

Conclusions

The findings of this project fail to reject the null hypothesis that there is no difference between tPA alone and the use of a combination of tPA and DNase to treat thoracic empyemas at OHSU hospital. These results were not statistically significant and need to be verified by a larger, prospective trial to be considered generalizable.

Introduction

Intrapleural infections are on the rise in the United States and the United Kingdom (Davies et al., 2010). An estimated 400,000 patients develop a pleural effusion each year (Light, 2006). Approximately 60,000 of these patients' pleural effusions progress to infections called thoracic empyemas, which means pus has

accumulated in the pleural space (Ferriero et al., 2014). With an adult mortality rate of approximately 16%, it is important to diagnose and treat these patients quickly and effectively (Iquina & Danckers, 2019). Treatment for these loculated infections includes draining the pleural fluid using either surgical methods or with chest tube drainage and the use of intrapleural fibrinolytics (Thommi et al., 2012). While the use of intrapleural fibrinolytics has long been an accepted treatment, there is no consensus directing the choice of which ones to use, what doses to use them at, and at what frequency to give them (Idell & Rahman, 2018). This problem is due to a lack of data. The largest randomized control trial to date is the multicenter intrapleural sepsis trial 2 (MIST 2) (Rahman et al., 2011). The MIST 2 trial identified that tPA alone was less effective than a combination of tPA-DNase at reducing length of stay (Rahman et al., 2011). Rahman et al. (2011) found that a combination of tPA and the enzyme dornase (DNase) was the best intrapleural treatment option for thoracic empyema in their study. However, this is only one trial with a sample size of 210, which draws into question the generalizability of its findings. Its outcomes must be recreated to ensure that they are accurate and safe for a larger portion of the population. Due to this lack of strong evidence supporting any one treatment regimen, medical providers often are left to make decisions based on personal preference along with current literature (Idell & Rahman, 2018). This project aims to compare the outcomes of patients with thoracic empyemas treated with tPA alone and patients treated with a combination of tPA and DNase at OHSU hospital.

Methods

This was a retrospective study that collected data using chart reviews on all patients who were treated for empyema using chest tube drainage and intrapleural fibrinolytics, either tPA or a combination of tPA and Dornase, between January and December of 2018 at OHSU hospital. These patients were identified using the following ICD codes: empyema with fistula (510.0, J86.0), empyema without fistula (510.9, J86.9), pleural effusion, infected (empyema) (511.1, J86.9), and empyema, tuberculosis (A15.6). This search identified 58 potential subjects to enroll in the study. Once these patients were identified, the researcher further narrowed the sample size to include only those patients that were treated using chest tube drainage and either intrapleural tPA or a combination of intrapleural tPA and DNase (tPA-DNase). The list was then narrowed by manually sorting through each of the 58 charts to identify if the patients had a chest tube placed and received intrapleural tPA or DNase.

The researcher then gathered demographic data (age and sex), the number of days the chest tube was in place, the type of fibrinolytic used (tPA or tPA-DNase), the dose of fibrinolytic used, and the number of doses each fibrinolytic was given. The number of days a chest tube was in place was used as another indicator of how long it took to resolve the infection. Chest tubes were removed once the infection had resolved, so if the patient's length of stay was prolonged due to another comorbidity, the number of days with a chest tube could be a more accurate representation of how long it took to actually clear the infection.

As mentioned earlier, there is no specific dose of tPA that is recommended, so providers use differing doses between patients. Therefore, this metric was

included to see if a lowest possible, effective dose of tPA could be identified. Similarly, the number of doses given in each group was recorded to see if one type of fibrinolytic required more doses than the other. This finding could impact the cost of treatment by extending the number of days with a chest tube, increasing length of stay or increasing cost of medication.

Patients' length of stay, resolution of the infection, and whether or not the patient required surgical intervention were recorded as the primary end points. The main goal of treating thoracic empyemas using intrapleural fibrinolytics is to resolve the infection and reduce the need for more invasive surgery. That is why these end points were chosen. Length of stay was chosen as an indicator to help determine if one medication was more effective at treating the infection than the other. These end points were also chosen because they are used in multiple other studies investigating intrapleural fibrinolytic treatment for thoracic empyemas (Bishwakarma et al., 2017; Popowicz et al., 2017; Rahmen et al., 2011).

Quantitative analysis was then performed using the Mann-Whitney U test to determine if there were statistically significant differences between the two treatment groups. This data could then be used by the providers treating thoracic empyemas at OHSU hospital to improve their practice. Due to the small sample sizes, non-parametric statistical tests were required for this data. The Mann-Whitney U test determines if there is a difference between two independent groups without assuming normal distribution. For this reason, the Mann-Whitney U test was chosen in place of the two-sample t-test. SPSS Statistics was the software used to perform all statistical analysis.

As no interventions were done, there are no major ethical implications in performing this retrospective review. To ensure the safety of patients and their private health information (PHI) included in the study, the OHSU hospital institutional review board reviewed and approved this project.

Results

A total of 16 participants were enrolled in the study, including ten males and six females. The average age was 64.4 years (SD 13.13) with the range being from 46 to 90 years of age at the time of treatment. All patients met enrollment criteria by being treated for thoracic empyema at Oregon Health & Science University hospital between January and December of 2018. Patients were not excluded based on comorbidities or other admitting diagnoses. The tPA only cohort was larger (n=12) than the tPA-DNase combination cohort (n=4). These small samples lead to a non-normal distribution requiring the use of non-parametric testing. All statistical tests were performed with a significance level of .05.

The median length of stay was 16.5 days (SD 13.98) for the tPA only group and 13.5 days (SD 3.30) for the tPA-DNase combination group (Table 1). The median number of days was chosen over the mean due to the difference in sample sizes between the two groups. The critical value obtained from the Mann-Whitney U two-tailed table was found to be 7 for the two sample sizes. This critical value was utilized as the cutoff for all Mann-Whitney U tests performed in this project. The Mann-Whitney U value for length of stay was 17.5. This non-statistically significant finding means that we fail to reject the null hypothesis that there is no group difference in the data (p=0.45).

Resolution of infection was determined if the patient did not require follow up treatment for a recurrence of the empyema within 3 months of discharge. Resolution of infection was chosen as an endpoint, because that is the primary goal of treatment. If one group was superior to the other in this category, it would be worth considering when choosing a treatment. The three-month time period was chosen because it is used in other similar studies. All sixteen participants in the project had a resolution of infection. No statistical tests were run on this data as there was no difference between the two cohorts in this project. A larger sample size may allow for better analysis of differences for this outcome.

The need for surgical intervention to clear the infection was included as a primary endpoint in this study also. One of the primary reasons to treat thoracic empyema with chest tube drainage is to prevent the need for surgery, which is more invasive and comes with a higher cost. However, no patient in either cohort required surgical decortication to resolve their infections. Similar to the resolution of infection findings, the difference between these two groups may be better understood with a larger sample size.

Other outcomes that were used to compare the two cohorts included the number of days with a chest tube and the number of doses used of each medication required. The number of days with a chest tube was included because the patients often had other reasons for hospitalization, which affected length of stay. Patients typically had their chest tube removed once the infection was considered to be resolved. Consequently, this may be a more accurate representation of how long it took to treat the empyema versus length of stay. The number of doses required for

each cohort was chosen as it plays a role in the cost of treatment and the number of days required to have a chest tube in place.

In the tPA group, the doses varied between 1mg and 10mg. Dosing remained consistent in the tPA-DNase cohort with 5mg of tPA and 10mg of DNase given to all 4 patients. Participants receiving tPA required an average of 3.08 doses (SD 1.79) given once daily. The cohort receiving tPA-DNase received on average 2.75 daily doses (SD 1.72). The average number of doses was used for this category as the data was much more normally distributed and had no outliers. The Mann-Whitney U test was again used to compare the two cohorts. The Mann-Whitney U failed to reject the null hypothesis that there is no evidence of a group difference in the data ($p= 0.95$).

Last, the number of days a patient had a chest tube in place was measured. The tPA cohort had a median of 8.5 days (SD 12.32), while the tPA-DNase cohort had a median of 6.5 days (SD 3.36). The Mann-Whitney U test failed to reject the null hypothesis that there is no evidence of a group difference in the data ($p= 0.26$).

Discussion

The data in this project fail to reject the null hypothesis that there was no difference between the tPA cohort and the tPA-DNase cohort in terms of length of stay, resolution of infection, need for surgical intervention, number of doses required to resolve the infection, or number of days with a chest tube. These findings differ from the previously mentioned MIST 2 trial, which showed the combination of tPA and DNase improved length of stay and reduced the need for surgery when compared to tPA alone (Rahman et al., 2011). However, the findings of this project were not statistically significant, which greatly limits their value.

One of the strengths of this study was the wide range of inclusion criteria that allowed patients not to be ruled out based on comorbidities or age. This provided our retrospective observations more strength. Including all patients regardless of comorbidities allowed for a more accurate depiction of the patient population at OHSU hospital.

Interpretation

When comparing lengths of stay, there was no evidence of a difference between the two groups. The p-value of 0.45 means that the results are not statistically significant. Similarly, the p-values for the number of doses given and the number of days with a chest tube were 0.95 and 0.26, respectively. These also indicate that the findings in this project were not statistically significant. This means that the authors are unable to reject the null hypotheses and also unable to accept that it is true. This leaves the findings with limited value as they cannot say definitively if one group outperformed the other.

The two variables that were found to have no difference between the cohorts were resolution of infection and the need for surgical intervention. Since the two cohorts had identical data, no statistical tests could be run. However, differences may be noted in a study with larger sample sizes.

The variation in dosing of tPA in the tPA only cohort could have affected the outcomes. Providers used doses ranging from 1mg to 10 mg but did not dictate a reason for giving a certain dose. A 6 mg dose was used on the most patients (n=7, 58.3%), while 2 mg was the second most frequently used dose (n=3, 25%). As no patients in the tPA cohort required surgical intervention, this could indicate that

lower doses of tPA can be equally effective. This finding should be validated in future studies.

The findings of this project did not align with the findings of the MIST 2 trial, which is currently the largest randomized control trial comparing tPA and a tPA-DNase combination. These differences may be due to the small sample size in this project versus the 210 participants in the MIST 2 trial (Rahman et al., 2011). Also, the treatment protocol in the MIST 2 trial included twice daily dosing rather than daily dosing (Rahman et al., 2011).

When compared to another small retrospective study (n=39) looking at tPA-DNase outcomes only, the results were more similar (Bishwakarma et al., 2017). The median number of doses given to the tPA-DNase group of this project was 3, while the average number of doses given to the patients in Bishwakarma et al. (2017) was 6. While the number of doses required was almost double, the length of stay between the two studies was similar. This variation in doses was likely due to twice daily dosing by Bishwakarma et al (2017). Bishwakarma et al. (2017) found the median length of stay to be 14.5 days. The data in this project found a median of 13.5 days in the tPA-DNase group. This mixture of results compared to other larger studies potentially confirms the flaw of having such a small cohort.

Due to the lack of statistically significant data, the findings of this project cannot be applied to patient care. This was a concern from the outset of the project because of the relatively low prevalence of thoracic empyema. This trade-off was made due to the time restrictions for this researcher to gather a larger amount of data.

Limitations

This single-center, retrospective project had several limitations. The most evident is the sample size. With only 16 participants, the generalizability of the findings would have been very limited regardless of statistical significance. This small sample was expected, due to the narrow time of 12 months and the relatively low incidence of thoracic empyema. The narrow window of the study was decided on to reduce the amount of variability in treatment regimen by the providers and to maintain a manageable number of participants for the researcher. However, even in this small timeframe there was variability in the dosage of tPA given in the tPA only cohort. Doses ranged from 1mg to 10 mg with 6mg being the most commonly given. The reason for this inconsistent dosing was not documented in the charts. This variation makes it difficult to home in on a specific dose of tPA being most effective.

Lastly, as this was a retrospective project, it relied on accurate charting by the medical providers. Some of the charting was inconsistent between providers and treatment teams, which limited the amount available data and required manual data extraction from each individual chart.

Future studies

The findings of this project show the need for more research regarding the use of tPA and tPA-DNase as treatment for thoracic empyemas. Future studies should be performed prospectively as large, randomized control trials. They should also look into the use of low dose tPA (less than 5mg) versus high dose tPA (10mg) versus a combination of 5mg tPA and 10mg DNase using the same outcomes as this project: length of stay, days with chest tube, and need for surgical intervention. This

will allow researchers to determine more accurately the best medication and dose with which to treat thoracic empyemas.

Conclusions

This small, retrospective project was unable to determine if the treatment of empyema with intrapleural tPA alone is as effective at resolving the infection and preventing the need for surgical intervention as the use of a combination of tPA and DNase in patients at OHSU hospital. Due to the lack of statistical significance and small sample size, these findings are not able to be used to direct patient care. The findings of this project need to be verified prospectively by a larger, randomized control trial before they can be considered as valid. Future studies should focus on comparing lower doses of intrapleural tPA against a combination of tPA and DNase to help determine the most effective treatment regimen for thoracic empyema.

Table 1. Group Data

Group	Average age	Male gender number (%)	Average number of doses	Median days w/ chest tube	Median length of stay	Resolution of infection number (%)
tPA only	63.8	8 (66.67%)	3.08 ± 1.8	8.5 ± 12.3	16.5 ± 13.9	12 (100%)
tPA-DNase	66	2 (50%)	2.75 ± 1.7	6.5 ± 3.4	13.5 ± 3.3	4 (100%)

Table 2. tPA Dosing Data

tPA dose given	No. of doses given among all patients	No. of patients receiving this dose	Avg. dose per patient
10 mg	6	1	6
6 mg	20	7	2.86
4 mg	4	2	2
2 mg	5	3	1.67
1 mg	2	1	2

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