Acta Medica Ruha
International Journal of Medicine and Health Sciences
E-ISSN: 2980-1184

ORIGINAL ARTICLE
Volume:2 Issue:3 Year:2024
https://doi.org/10.5281/zenodo.13751912

Comparison of the Efficacies of Alteplase and Streptokinase Used for Fibrinolytic Treatment in Parapneumonic Pleural Effusion and Empyema

Parapnömonik Plevral Efüzyon ve Ampiyemde Fibrinolitik Tedavide Kullanılan Alteplaz ve Streptokinazın Etkinliklerinin Karşılaştırılması

Şamil Günay[1], Ahmet Acıpayam[1]

[1]Department of Thoracic Surgery, Antalya City Hospital, Antalya, Türkiye

ABSTRACT

Introduction: Used rarely in the fibrinolytic treatment of parapneumonic pleural effusion (PPE) and empyema, alteplase is a plasminogen activator (tPA) analogue.
Objective: In our study, we divided the patients with PPE and empyema, to whom we implemented video-assisted thoracic surgery, into two groups and we implemented VATS to one group and alteplase plus fibrinolysis following VATS to the other. We compared these two groups through clinical and biochemical parameters.
Methods: Totally 66 patients were involved in the study. The patients were divided into 2 groups randomly. 5-20 mg alteplase was administered to 40 patients in the first group (Alteplase) through tube thoracostomy following VATS. And only VATS was implemented to 26 patients in the second group (Control). The chest tube removal times of the patients and their lengths of hospitalization, C-Reactive Protein (CRP) and White Blood Cells (WBC) values were compared statistically.
Results: It was determined that the groups were homogeneous statistically (P>0.05), CRP values (11.99±9.63) in the alteplase group were statistically significantly higher comparing to the control (4.07±5.10) group (P<0.05), Alteplase group was better in the comparison of the removal times of chest tubes, lengths of hospitalization and WBC values, however the findings were not statistically significant (P>0.05).
Conclusion: Alteplase is a significantly efficient fibrinolytic treatment with a success rate of 87.5%, which can be used in PPE and empyema with minimum side effects in appropriate dosages.

Keyswords: Alteplase, Streptokinase, Fibrinolytic Treatment, Parapneumonic Pleural Effusion, Empyema.

ÖZET

Giriş: Parapnömonik plevral efüzyon (PPE)ve ampiyemin fibrinolitik tedavisinde nadir kullanılan alteplaz, plazminojen aktivatör (tPA) analoğudur.
Amaç: Çalışmamızda Video yardımlı göğüs cerrahisi (VATS) uyguladığımız PPE ve ampiyemli hastaları 2 gruba ayırdık, bir gruba sadece VATS, diğer gruba VATS sonrası alteplaz ile fibrinolizis uyguladık. Bu iki grubu klinik ve biyokimyasal parametrelerle karşılaştırdık.
Metod: Toplam 66 hasta çalışmaya alındı. Hastalar rastgele seçilerek 2 gruba ayrıldı. Birinci grupta (Alteplaz) bulunan 40 hastaya VATS sonrası 5-20 mg alteplaz göğüs tüpü içinden uygulandı. İkinci gruptaki (Kontrol) toplam 26 hastaya sadece VATS yapıldı. Hastaların göğüs tüpü çekilme süreleri, hastanede kalış süreleri, C-Reaktif Protein (CRP)ve White Blood Cells (WBC) değerleri istatistiksel olarak karşılaştırıldı.
Bulgular: Grupların istatistiksel olarak homojen olduğu (P>0.05), Alteplaz grubundaki CRP (11,99±9,63) değerlerinin, kontrol (4,07±5,10) grubuna göre daha fazla olmasının istatisitksel olarak anlamlı buluğu (P<0.05), göğüs tüpü çekilme süreleri, hastanede kalış süreleri ve WBC değerlerinin karşılaştırılmasında Alteplaz grubunun daha iyi olduğu ama bulguların istatistiksel olarak anlamlı olmadığı tespit edildi (P>0.05).
Sonuç: Alteplaz PPE ve ampiyemde kolay kullanılabilecek, uygun dozlarda minimal yan etkileri olan, %87,5 başarı ile önemli ölçüde etkili fibrinolitik bir tedavidir.

Anahtar Kelimeler: Alteplase, Streptokinaz, Fibrinolitik Tedavi, Parapnömonik Plevral Efüzyon, Ampiyem.

INTRODUCTION

Parapneumonic pleural effusion (PPE) is the most frequent reason of the exudative pleural fluids that cause to inflammation of pleural capillary endothelium and permeability increase (1,2). Delay in the initiation of therapy leads to reproduction of fibrin tissues, defense cells, bacteria and bacterial products in the pleural space. As a result, serious situations may occur such as trapped lung, lung abscess, fistula, sepsis, complicated PPE or empyema (3,4). The first treatment choice of these diseases is the use of

Corresponding Author: Şamil Günay, e-mail: samilgunay@yahoo.com
Received: 26.07.2024, Accepted: 10.09.2024, Published Online: 20.09.2024
Cited: Günay Ş, et al. Comparison of the Efficacies of Alteplase and Streptokinase Used for Fibrinolytic Treatment in Parapneumonic Pleural Effusion and Empyema. Acta Medica Ruha. 2024;2(3):193-198. https://doi.org/10.5281/zenodo.13751912

antibiotics. In case of complicated situations with the progression of the disease, surgery and fibrinolytic therapies become the part of the treatment (3-5). The stage when fibrinolytic treatment is beneficial most is the fibrinopurulent phase of PPE and empyema (4,5). We can consider streptokinase, urokinase, deoxyribonuclease (DNaz) and rarely the tissue plasminogen activators (tPA) among the fibrinolytic agents used at this stage (7,8). Streptokinase is an active fibrinolytic agent that is frequently used in the thoracic surgery (7-9). Due to the decrease in streptokinase production, studies have been performed to search for alternative fibrinolytic agents in recent years. Among these agents, alteplase is a 2nd generation thrombolytic and fibrin selective agent, which is most frequently used as tPA (9,10). It affects by reducing fibrinogen and plasminogen (10). While studies about the fibrinolytic treatment with alteplase are extensive, such studies are limited for adult patients (6,9).

We designed a retrospective study to evaluate the efficacy and reliability of alteplase in fibrinolytic treatment. We divided the patients with PPE and empyema, to whom we implemented chest drain, into 2 groups and administered fibrinolysis with streptokinase to one group and with alteplase to the other and compared the groups with clinical, radiological and biochemical parameters.

METHODS

Patients with pleural effusion to fill at least one third of a hemithorax in the chest radiography and pleural fluid pH lower than 7.2, at whom multiple septations were determined in their thorax ultrasound, between the dates of March 2014 and March 2015 were involved in the study. The patients were divided into 2 groups indiscriminatingly. There were 10 (25%) females and 30 (75%) males, 40 patients in total, in the alteplase group. 32 F chest drain was implemented to the patients in this group with local anesthesia and left to closed underwater drainage. Starting from the postoperative 2nd day, 5-20 mg alteplase (0.1 mg/kg) + 50 cc saline solution was administered through the chest drain into intrapleural space once a day in 3 or 5-day periods. The drain was held flapped for 2 hours. The dosage of alteplase was arranged according to the weight, anticoagulant used and general status of the patient.

There were 10 female (38.5%) and 16 (61.5%) male, 26 patients in total in the streptokinase group. 32 F chest drain was implemented to the patients in this group with local anesthesia and left to closed underwater drainage. Starting from the postoperative 2nd day, 250.000 I.U streptokinase (concentration of 10 IU/mL) + 50 cc saline solution was administered through the chest drain into intrapleural space once a day in 3 or 5-day periods. The drain was held flapped for 2 hours.

Gender, ages, complications, malign and benign characteristics of the patients, chest tube removal times, durations of hospital stay were measured before the treatment and C-Reactive Protein (CRP) and White Blood Cells (WBC) values were measured on the postoperative 7th day. These values were compared statistically. Patients without fever and whose CRP levels were normal in their follow up periods were accepted successful.

Statistical Analyses

SPSS 22.0 (IBM Corparation, Armonk, New York, United States) and PAST3 (Hammer, Ø, Harper, D.A.T., Ryan, P.D. 2001) paleontological statistics programs were used in the analysis of the data. Conformity of univariate data to normal distribution was tested through Shapiro-Wilk test, Mardia (Dornik and Hansen Omnibus) test was used for the conformity of multivariate data to normal distribution and Leneve test was used for the variance homogeneity. Independent-Samples T test was used in the comparison of two independent groups together with Bootstrap results. General Linear Model-Repeated Anova test was used together with the Bootstrap results for analyzing the two repetitive measurement of dependent variables and the interaction of the repetitive measurements of the variable according to groups. Fisher Exact test was used in the comparison of categorical data with each other through Monte Carlo Simulation method. The quantitative data was expressed in the tables as mean ± sd. (standard deviation) and Range (Maximum-Minimum) values. The categorical data was expressed as numbers (n) and percentages (%). The data was analyzed at 95% confidence interval and the p value less than 0.05 was accepted significant.

RESULTS

Totally 66 patients, 20 (30.3%) females and 46 (69.7%) males, with the mean age of 43.55 ± 20.37 (85-4), who were implemented chest drain with the diagnoses of PPE and empyema between the dates of March 2014 and March 2015 were involved in the study (Table 1).

Table 1. Demographic Features of the Study Groups

	Control (n=26)	Alteplase (n=40)	Total (n=66)	P [a]
Age	47.85±20.36(85-21)	40.75±20.40 (69-4)	43.55±20.37 (85-4)	0.346
Sex (female/ Male)	10(38.5) / 16(61.5)	10(25) / 30(75)	20(30.3) / 46(69.7)	0.461
Right/Left	18(69.2) / 8(30.8)	20(50) / 20(50)	38(57.6) / 28(42.4)	0.310
Benign / Malignant	20(76.9) / 6(23.1)	36(90) / 4(10)	56(85.9) / 10(15.1)	0.276

General Linear Model Repeated Anova (Wilks' Lambda) (Bootstrap) - Independent T Test (Bootstrap) - Fisher Exact Test (Monte Carlo) Mean± Standard deviation Range (Maximum- Minimum).

It was determined that the groups were homogeneous in the demographic examination made in terms of Gender, age, side of pleural effusion and the histopathology of the effusion (benign, malign) ($p > 0.05$) (Table 1). Any difference was not seen between the groups in terms of numbers and values.

The CRP mean value of the alteplase group before treatment was measured as 16.77 ± 10.01 mg/L (43.7-4.9), and as 4.78 ± 4.15 mg/L (16.3-0.96) on the postoperative 7th day. The difference between these two values was found as 11.99 ± 9.63 mg/L and this decrease in CRP was found statistically significant ($p < 0.001$). The CRP mean value of the streptokinase group before treatment was measured as 8.92 ± 6.80 mg/L (25.6-1.65) and as 4.85 ± 2.97 mg/L (12.1-1.1) on the postoperative 7th day (Table 2). The difference between these two values was found as 4.07 ± 5.10 mg/L and this decrease in CRP was found statistically significant ($p = 0.014$). This decrease in the CRP values was found statistically significantly higher in the alteplase group ($p < 0.05$). It was determined that alteplase decreased the CRP more and recovered the infection clinics of patients better.

Table 2. WBC and CRP Value Alterations in Durations of Hospital Stay and Chest Withdrawal Times

	Control (n=26)	Alteplase (n=40)	Total (n=66)	P [a]
The durations of hospital stay	12±4.12(21-7)	11.5±3.98(21-7)	11.7±3.98(21-7)	.730
The durations of hospital stay	10.46±3.64(18-6)	10.25±3.91(19-5)	10.33±3.75(19-5)	.877
WBC				
Before(B)	11.68±5.48(24.1-5.7)	14.77±4.74(24.2-5.3)	13.55±5.19(24.2-5.3)	.115
Last(L)	8.45±2.12(12.8-5.1)	9.57±2.50(14.3-5.5)	9.13±2.39(14.3-5.1)	
Difference (B-L)	3.23±4.41(12.9-(-0.8))	5.20±4.47(13.2-(-4.8))	4.42±4.48(13.2-(-4.8))	.225
P [b]	0.022	<0.001	<0.001	
CRP				
Before(B)	8.92±6.80(25.6-1.65)	16.77±10.01(43.7-4.9)	13.68±9.59(43.7-1.65)	.015
Last(L)	4.85±2.97(12.1-1.1)	4.78±4.15(16.3-0.96)	4.81±3.68(16.3-0.96)	
Difference (B-L)	4.07±5.10(17.5-(-0.4))	11.99±9.63(36.9-(4.6))	8.87±8.96(36.9-(-4.6))	.011
P [b]	0.014	<0.001	<0.001	

General Linear Model Repeated Anova (Wilks' Lambda) (Bootsrap) - Independent T Test (Bootsrap) - Fisher Exact Test (Monte Carlo) Mean± Standard deviation Range (Maximum-Mnimum).

The WBC mean value of the alteplase group before treatment was measured as 14.77 ± 4.74 K/mm3 (24.2-5.3), and as 9.57 ± 2.50 K/mm3 (14.3-5.5) on the postoperative 7th day. The difference between these two values was found as 5.20 ± 4.47 K/mm3 and this decrease in WBC was found statistically significant ($p < 0.001$). The WBC mean value of the streptokinase group before treatment was measured as 11.68 ± 5.48 K/mm3 (24.1-5.7) and as 8.45 ± 2.12 K/mm3 (12.8-5.1) on the postoperative 7th day. The difference between these two values was found as 3.23 ± 4.41 and this decrease in WBC was not found statistically significant ($p < 0.05$). This decrease in the WBC values was found statistically significantly higher in the alteplase group ($p > 0.05$) (Table 2).

The durations of hospital stay were found as 11.5 ± 3.98 days in the alteplase group and 12 ± 4.12 days in the streptokinase group. The durations of hospital stay of the patients in the alteplase group to be lesser was not found statistically significant ($p = 0.730$) (Table 2). The drain removal times of the alteplase group were found as 10.25 ± 3.91 days and 10.46 ± 3.64 days in the streptokinase group. It was not found statistically significant the removal times of the drains to be lesser in the alteplase group ($p= 0.877$) (Table 2).

It was provided recovery in 35 (87.5%) patients in the alteplase group, it was failed in 5 (12.5%) patients (Table 3). Decortication and resection plus decortication (broncho-pleural fistula and intraparenchymal abscess) had to be implemented respectively for 2 and 3 of the 5 patients for whom it could not be provided recovery and none of the patients died during and after the treatment. When it was provided recovery in 21 (80%) patients in the streptokinase group, it was failed in 5 (20%) patients (Table 3). Decortication and resection plus decortication (broncho-pleural fistula and intraparenchymal abscess) had to be implemented respectively for 2 and 3 of the 5 patients for whom it could not be provided recovery and none of the patients died during and after the treatment.

Table 3. Efficacy of Alteplase and Streptokinase.

Parapneumonic effusions and emphyema	Alteplase	Success (n=35 ,87%)	
		Failed (n=5, 13%)	Decortication n=2
			Resection n=3
	Streptokinase	Success (n=21 ,80%)	
		Failed (n=5, 20%)	Decortication n=2
			Resection n=3

DISCUSSION

Streptokinase is the most commonly used fibrinolytic agent in recent years. Due to the decrease in streptokinase production, the alternative agents of tPA and DNAaz have started to be preferred. alteplase is a tPA that has a high fibrin affinity. Because of being a fluid, it can be used easily through the chest drain. In our study, we deemed suitable the use of alteplase, a fibrin specific agent that is easy to implement and used frequently in thromboembolism, in the comparison with streptokinase.

Our experiences with alteplase showed that there was not a definite standard to be implemented in patients. The dosage of alteplase may be adjusted can be arranged according to the weight of the patient, anticoagulant and antiaggregant (acetylsalicylic acid, warfarin) treatment used and the general status and biochemical parameters of the patient (5-10 mg). A minimal hemorrhage can be seen in patients' implemented alteplase and it can be useful to make hemogram examinations frequently in such patients. Blood transfusion was not needed in any of our patients. In the study they performed on tPA, Froudarakis et al emphasized that there was a significant decrease in WBC and CRP levels of the patients in the group they implemented tPA, they determined a rapid recovery in the clinical course of these patients and the durations of hospital stay had shortened (11). In our study, rapid reductions in CRP values were determined in both groups.

There were rapid reductions in the CRP values of both groups in our study. The more reduction in the alteplase group was statistically significant. It was determined with the clinical observations that the recovery was faster in this patient group. Also, it was seen that the WBC values decreased in both groups; however the more reduction in the alteplase group was not statistically significant.

There are studies in the literature which state that the fibrinolytic agents were effective macroscopically in the resolution of intrapleural fluid collection macroscopically, increased the pleural drainage amount and reduced the need for decortication (12). In our study, successes were achieved at the rates of 87.5% and 80% respectively in the alteplase and Streptokinase group. It was determined that the alteplase group had a better success rate and required less large surgical interventions.

Upon the determination that the viscosity of the empyema fluid was caused by the DNA; it was seen that the intrapleural application of the DNAaz enzyme would reduce the fluid viscosity and support the pleural drainage. In their study, Rahman et al divided 210 patients into 4 groups indiscriminatingly and administered 10 mg tPA to 1st group, DNAaz to 2nd, tPA and DNAaz to 3rd and double placebo to 4th group. They reported that the tPA-DNAaz group showed better results in the radiological pleural opacity resolution, necessity of surgical intervention and duration of hospital stay (8). Davied et al emphasized

that the daily drainage had increased significantly following the intrapleural fibrinolytic application comparing to the group where fibrinolytic agents were not used, and the radiologic recovery was better in the fibrinolytic implemented group (13). In our study, it was determined that the durations of hospital stay and the drain removal times were lesser in the alteplase group, however, there was no statistically significant difference between the groups ($p > 0.05$). Due to any data was not collected for the daily drainage amounts; there is no comment in this particular in our study.

The adverse effects of the fibrinolytic treatment were reported as chest pain, fever, allergic reaction and pleural bleeding (14,15). In the study they performed with tPA, Froudarakis et al determined bleeding in 3 and pain complications in 4 patients (11). In their study, Gervais et al reported that the intrapleural tPA application caused to pleural bleeding in a patient who received systemic anticoagulation (16). Taylor et al. stated that complications developed in 28 (38%) patients in a study about the effects of alteplase treatment in children with PPE and empyema. They reported that pain (21%, n = 15) ranked first and saturation reduction ranked number two among these complications (9). In our study, 700-1000 mL/day hemorrhages, which continued for 3 days, were determined from the drains of 3 patients who were administered 20 mg alteplase. A 0.2-0.4 g/dL of change was seen in the hemogram values of these patients. Blood transfusion was not performed in none of these patients. The use of 10 mg alteplase was determined to be safer in patients using anticoagulants such as acetylcysteine or warfarin due to any disease.

Limitations of the study is the retrospective design and the number of cases is relatively low.

CONCLUSION

We prepared a retroprospective study on the purpose of comparing the efficacies of alteplase and streptokinase in the fibrinolytic treatment. We compared these two groups through clinical, and biochemical parameters. In consequence of our study, we determined that (i) the (CRP) alteplase group was more effective in terms of infection control, (ii) there was not any difference between the groups in terms of duration of hospital stay, (iii) there was not any difference between the groups in terms of chest drain removal time and (iv) the 2nd surgery was needed lesser in the alteplase group.

In conclusion, with minimal side effects in proper dosages and 87.5% success, alteplase is a considerably effective fibrinolytic treatment that can easily be used in PPE and empyema.

DESCRIPTIONS

No financial support.

No conflict of interest.

Acknowledgement: The authors would like to thank the patients for granting permission for their hospital data to be included in this paper, and also Dr. Dragan Danilovski for his assistance in the statistical analyses.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

REFERENCES

1. Noppen M, De Waele M, Li R, Gucht KV, D'Haese J, Gerlo E et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med. 2000;162:1023-1026.

2. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population-based analysis. J Thorac Cardiovasc Surg. 2007;133:346-351.

3. Maskell NA, Davies CW, Nunn AJ, et al. First Multicenter Intrapleural Sepsis Trial (MIST1) Group. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;352:865-874.

4. Heffne JE, Klein JS, Hampson C. Interventional management of pleural infections. Chest. 2009;136:1148-1159.

5. Chapman SJ, Davies RJ. Recent advances in parapneumonic effusions and empyema. Curr Opin Pulm Med. 2004;10:299-304.

6. Generali JA, Cada DJ. Alteplase: pleural effusion (parapneumonic) and empyema in children. Hosp Pharm. 2013;48:912-921.

7. Thommi G, Nair CK, Aronow WS, Shehan C, Meyers P, McLeay M. Efficacy and safety of intrapleural instillation of alteplase in the management of complicated pleural effusion or empyema. Am J Ther. 2007;14:341-345.

8. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365:518-526.

9. Taylor JL, Liu M, Hoff DS. Retrospective analysis of large-dose intrapleural alteplase for complicated pediatric parapneumonic effusion and empyema. J Pediatr Pharmacol Ther. 2015;20:128-137.

10. Yasar A S, Bicer A, Turhan H, Sasmaz H. Third Generation Thrombolytic Agents in the Guidance of Trials. Arch Turk Soc Cardiol. 2004;32:564-570.

11. Froudarakis ME, Kouliatsis G, Steiropoulos P, et al. Recombinant tissue plasminogen activator in the treatment of pleural infections in adults. Resp Med. 2008;102:1694-1700.

12. 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.

13. Davies RJO, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. Thorax. 1997;52:416-421.

14. Bouros D, Schiza S, Tzanakis N, Chalkiadakis G, Drositis J, Siafakas N. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, doubleblind study. Am J Respir Crit Care Med. 1999;159:37-42.

15. Ozcelik C, Inci I. Nizam O, Onat S. Intrapleural fibrinolytic treatment of multiloculated postpneumonic empyemas. Ann Thorc Surg. 2003;76:1849-1853.

16. Gervais DA, Levis DA, Hahn PF, Uppot RN, Arellano RS, Mueller PR. Adjunctive intrapleural tissue plasminogen activator administrated via chest tube placed with imaging guidance: effectiveness and risk for hemorrhage. Radiology. 2008;246: 956-963.