Research Article/Araştırma Makalesi

EFFECTIVENESS OF INTRAPLEURAL FIBRINOLYTIC THERAPY

İNTRAPLEVRAL FİBRİNOLİTİK TEDAVİ ETKİNLİĞİ

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Abstract

Objectives: Fluids filling the complicated pleural space may disrupt the normal function of the lung and require medical or surgical intervention. Streptokinase or Tissue Plasminogen Activator (tPA) acts by breaking down fibrin and some other proteins, and with intrapleural fibrinolytic therapy (IPFT) performed at the appropriate time, this process can be interrupted, the development of fibrous crust on the lung can be prevented, and the patient can be saved from undergoing more invasive procedures. **Method:** In this study, 280 cases who underwent IPFT with tube/catheter thoracostomy between 2003 and 2020 were reviewed retrospectively. Fibrinolytic agent dissolved in 100 cc saline was administered through the intrapleural space via tube or catheter thoracostomy. Thoracostomy tube or catheter was clamped for 1-4 hours to ensure optimum effect. Then, the clamp was opened, and the patient was followed up with close drainage. As an IPFT agent in 100 cc of saline solution, 250000 IU of streptokinase or daily doses of 5-10mg Tissue Plasminogen Activator (tPA) was applied. **Results:** A total of 280 patients (195 (69.6%) male and 85 (30.6%) female) with a mean age of 51.5 (5-86) years underwent IPFT. Streptokinase was applied through the pleural space to 85 (30.3%) and Tissue Plasminogen Activator (tPA) to 195 (69.7%) cases. After this treatment, complete response was obtained in 252 and partial response in 11 patients. As complications, intrapleural bleeding was observed in 12 and aseptic pouch in 13 cases. The success of the treatment was determined as 90 percent. **Conclusion:** Instead of more invasive surgical procedures in the treatment of non-draining complicated pleural effusion, IPFT is a safe, effective, and highly successful procedure with a lower side effect profile.

Keywords: Intrapleural fibrinolytic, Streptokinase, Tissue plasminogen activator (tPA), Pleural effusion

Özet

Giriş: Komplike olmuş plevral aralığı dolduran sıvılar akciğerin restriksiyonuna neden olarak ekspansiyonunu engeller. Böylece akciğerin normal işlevini bozarak müdahale gerektirecek duruma gelmesine neden olabilirler. Streptokinaz ya da Tissue Plazminojen Activatörü (tPA) intra plevral boşluğa verilerek bu alanda oluşan fibrin ve diğer bazı proteinleri parçalayarak etki eder. Uygun zamanda yapılan intraplevral fibrinolitik tedavi (IPFT) ile fibrin oluşma süreci kesintiye uğratılır. Böylece akciğer üzerinde fibröz kabuk gelişimi önlenerek hasta daha invaziv işlemlerden kurtarılabilir. **Metot:** Bu çalışmada 2003-2020 yılları arasında komplike olmuş plevral aralığı dolduran sıvılar için tüp veya kateter torakostomisi ile IPFT uygulanan 280 olgu retrospektif olarak incelendi. Fibrinolitik ajan, 100 cc serum fizyolojik içerisinde tüp veya kateter torakostomi aracılığı ile intraplevral boşluğa verildi. Optimum etkiyi sağlamak için tüp veya kateter torakostomi 1-4 saat klemplendi. Sonrasında klemp açılarak yakın drenaj takipleri yapıldı. IPFT ajanı olarak 100 cc SF içinde 250000 IU streptokinaz veya 5-10mg/gün Tissue Plazminojen Activatörü (tPA) uygulandı. **Bulgular:** IPFT uygulanan 280 hastanın 195'i (%69.6) erkek, 85'i (%30.6) kadın hastaydı. Hastaların ortalama yaşı 51.5 (en küçük 5y ve en büyük 86y) olarak hesaplandı. Plevral aralıktan 85 (%30.3) olguya streptokinaz, 195 (%69.7) olguya Tissue Plazminojen Activatörü (tPA) uygulandı. Uygulanan bu tedavi sonrası hastaların 252'sinde tam yanıt, 11'inde kısmi yanıt alınırken, tedavi uygulanmasına rağmen 17 hastada tedaviye yanıt alınamadı. Komplikasyon olarak hastaların 12'sinde intraplevral kanama ve 13'ünde aseptik poş gözlendi. Uyguladığımız bu tedavinin başarısı %90 olarak belirlendi. **Sonuç:** Drene olmayan komplike plevral efüzyon tedavisinde daha invazif cerrahi girişimler yerine IPFT güvenli, etkili ve yan etkisi az başarısı yüksek , bir uygulamadır.

Anahtar kelimeler: İntraplevral fibrinolitik, Streptokinaz, Tissue plazminojen aktivatörü (t-PA), Plevral efüzyon.

1. INTRODUCTION

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Activation of the plasminogen-plasmin system provides degradation and polymerization of fibrin. Activation of this system is either through a factor 12-into two groups extrinsic (tissue) and intrinsic (vessel wall) activators (**Figure 1**). Although the treatment and approach protocols vary according to the etiology of the pleural effusion developed, the generally applied treatment methods are; pleural drainage methods such as the application of catheter/tube thoracostomy into the pleural space, parenteral antibiotic treatments, surgical interventions such as IPFT, video thoracoscopic surgery (VATS) or thoracotomy. IPFT, which combines medical or interventional methods, is the treatment with fibrinolytic agents delivered into the intrapleural space according to the etiology of the effusion. Intrapleural fibrinolytic therapy (IPFT) provides drainage in complicated pleural fluids that cannot be drained by conventional methods and prevent patients from resorting to more aggressive diagnostic and treatment methods (1).

dependent pathway or with the aid of plasminogen activators (PAs). Plasminogen activators are divided

Fluids filling the complicated pleural space may disrupt the normal function of the lung and require intervention. Adequate and complete drainage may not be achieved with catheter/tube thoracostomy. A fibrous crust may form over the lung within 7-10 days in blood, clots, empyema, and benign or malignant pleural fluids that cannot be drained effectively and ultimately cause lung restriction and prevent its expansion. Streptokinase or Tissue Plasminogen Activator (tPA) acts by breaking down fibrin and some other proteins, and this process can be interrupted by IPFT performed at the appropriate time. The development of fibrous crust on the lung can be prevented, thereby saving the patient from the application of more invasive procedures.

Figure 1: Mechanism of fibrin formation

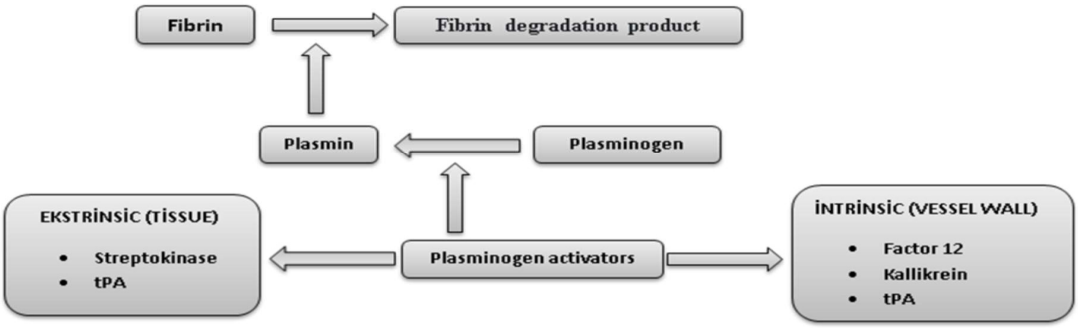
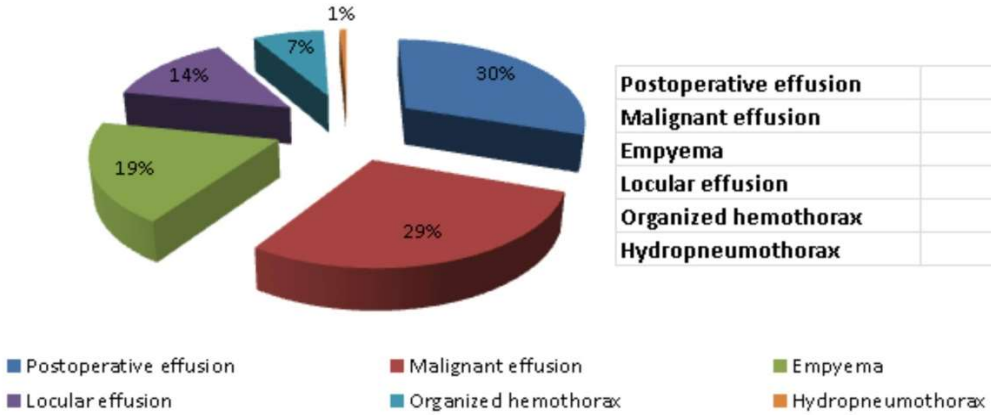


Figure 2:. Diagnoses and distribution of patients who underwent IPFT



Postoperative effusion	85
Malignant effusion	81
Empyema	53
Locular effusion	38
Organized hemothorax	21
Hydropneumothorax	2

2. METHODS

In this study, 280 cases who underwent IPFT with tube or catheter thoracostomy between 2003 and 2020 were reviewed retrospectively. Our cases were evaluated in terms of age, gender, indications for applied procedures, application methods, response to treatment, and complications. IPFT was planned for the cases where complete drainage could not be achieved with catheter or tube thoracostomy, and clinical and radiological improvement was not detected. Streptokinase (250000 IU/day) or Tissue Plasminogen Activator (tPA) (5-10 mg/day) were used as IPFT agents. One of them was reconstituted with 100 cc saline solution and applied through the intrapleural cavity by tube or catheter thoracostomy. Then catheter was clamped for 1-4 hours to ensure the optimum effect of the drug. During this period, the patient's positions were changed to allow the agent to penetrate the intrapleural space better. Then the clamp was opened, and the patient was followed up with close drainage. Intrapleural fibrinolytic agents were administered to the cases 1-7 times on average.

3. RESULTS

A total of 280 patients [195 (69.6%) malesand 85 (30.6%) females] with a mean age of 51.5 years range, 5-86yearsunderwent IPFT. Catheter thoracostomy was performed in 114 (40.7%), and tube thoracostomy in 166 (59.3%) cases. These patients received IPFT with the indications of postoperative pleural effusion (n=85), malignant pleural effusion (n=81), empyema (n=53), loculated pleural effusion (n=38), organized hemothorax (n=21), and hydropneumothorax (n=2) (**Figure 2**). Streptokinase was applied to 85 (30.3%) cases, and Tissue Plasminogen Activator (tPA) was applied to 195 (69.7%) cases through the pleural space. After this treatment, complete response was obtained in 252 and partial response in 11 patients. Treatment of 17 patients who were unresponsive to IPFT was completed with VATS (n=10) or thoracotomy with pleural debridement (n=7). As complications, intrapleural bleeding was observed in 12 and aseptic pouch in 13 cases. Among patients who developed intrapleural hemorrhage, only 4 cases required blood transfusion. These patients' treatment was interrupted, and supportive care with erythrocyte suspension was provided.

The criteria for unresponsiveness to treatment were determined as the treatment-refractory active drainage, lack of clinical and radiological improvement, failure to restore normal lung capacity, and the presence of a pouch on the drained side despite drainage. Treatment response in patients who underwent IPFT was evaluated with PA AC radiographs. The success of the treatment was determined as 90%.Only 6% of the patients did not respond to the treatment. Those patients' treatment was achieved with surgical interventions (**Table 1**).

Table 1. Distribution of responses to treatment

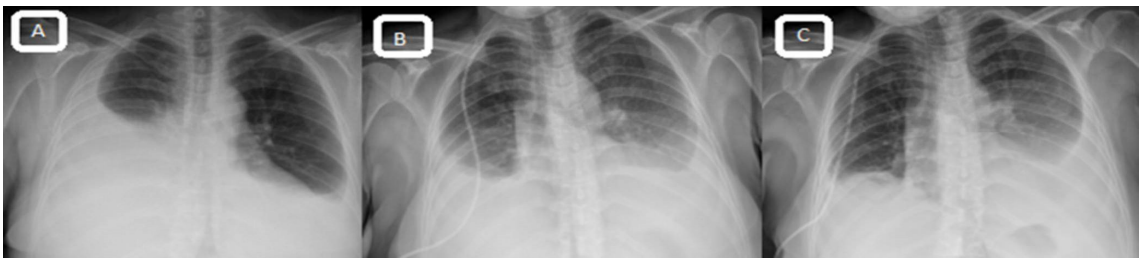
Response to treatment	Number (n)	Percent (%)
Full response	252	90%
Partial response	11	4%
Unsuccessful	17	6%

4. DISCUSSION

The most common causes of malignant pleural effusions are lung cancer in men and pleural effusions due to breast cancer in women. The most common cause of benign pleural effusions is parapneumonic effusions. The incidence of parapneumonic effusion in patients hospitalized for pneumonia and receiving treatment is 20 to 40 percent (3). The incidence of empyema among these patients ranges between 1 to5 percent (4). Intrapleural fibrinolytic treatment is often effective in complicated pleural effusions refractory to medical treatment or those that cannot be drained by catheter thoracostomy.
The most commonly used agents are streptokinase, urokinase, and tissue plasmogen activator (tPA). Streptokinase is a protein with a half-life of 18-83 minutes, and group C beta-hemolytic streptococci synthesize it. It manifests its effect by binding to the plasminogen proactivator and converting inactive plasminogen to active plasmin. Activated plasmin also breaks down fibrin. Urokinase is an enzyme synthesized by the kidney and exerts its effect by directly converting plasminogen to active plasmin. Tissue plasminogen activator is an endogenously and recombinantly produced agent with a half-life of 5-72 minutes and shows its effect by activating fibrin-bound plasminogen. (5).

As a very effective method, the success of IPFT is reported to be in the range of 80-94 percent in the literature reviews. Ulutaş et al. applied IPFT to 85 patients with had a postprocedural success rate of 91.8 percent (1). Similarly, Robinson et al. (n=13), Inci et al. (n=24), and Thommi et al. reported postprocedural success rates of 77%, 91.7%, and

Figure 3: Effusion that did not regress (B) despite the application of pleurecan in a patient with a diagnosis of ovarian cancer (A) and PA AC X-ray after IPFT (C)



85%, respectively (6,7,8). In our study, in line with the literature, the complete response rate to treatment was 90% in patients who underwent IPFT too. In many studies conducted on different groups, varying results have been obtained in parameters such as response to treatment, clinical improvement, or reduced need for surgery. In a randomized controlled study conducted by Tunçözgür et al., intrapleural urokinase was administered to 24 of 49 patients and intrapleural saline to 25 of them. As a result, the authors had found that the fluid drainage significantly increased, the length of hospital stay decreased, and the need for surgery decreased in the group treated with urokinase (9). Contrary to this,in a study conducted by Maskell et al. (MIST1 group), 427 patients were divided into intrapleural streptokinase and saline placebo groups. No difference was observed between groups in terms of mortality, need for surgery, radiological outcome, and hospital stay (10). Similarly, Cameron et al. reviewed data analysis of 761 cases included in the Cochrane database in 2008 and had not observed any decrease in mortality in the group receiving intrapleural fibrinolytic therapy (11). In a retrospective study conducted by Skeete et al. on 41 patients, radiological regression was observed with tPA application in 79% of the patients, the need for surgery was eliminated in 78% of the patients, and surgery was performed in 2 patients with hemothorax (12). In our study, the need for surgery decreased considerably after IPFT, and only 6% of the patients were operated due to unresponsiveness to treatment. Fibrinolytic therapy's common side effects are chest pain, fever, allergic reaction, and intrapleural bleeding. (13). The most common complication of IPFT is intrapleural bleeding. The incidence of intrapleural bleeding in patients receiving IPFT has been reported to 1.8 to 12 percent (14-17). Abu Daft et al. reported that pleural bleeding developed in 15 patients in their series of 237 patients, and emergency thoracotomy was required in 3 patients (18). In our study, intrapleural hemorrhage developed in 12 (4.2%) patients who underwent IPFT, and blood transfusion was required in 4 cases. Bleeding was controlled by interrupting the treatment. Despite the possibility of complications, IPFT is a safe treatment method. Publications show that it can be used safely in pregnant women and children (19).

5. CONCLUSION

IPFT can be applied before surgical interventions when loculated empyemas, organized hemothorax-hematomas, densely fibrinous and non-draining malignant-benign pleural effusions. It is a safe, effective, and highly successful procedure with a lower side-effect profile. It still maintains its effectiveness as an alternative to surgery.

Conflict of Interest: The authors declare that no conflict of interest.

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