

Case Series

Intrapleural Tenecteplase for Complicated Parapneumonic Pleural Effusion

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Intrapleural thrombolytics have shown promising results in complicated parapneumonic pleural effusions reducing the need for surgical interventions. Until now, studies have evaluated primarily streptokinase, urokinase, and recently, alteplase. In this case series, we share our experience with tenecteplase—a tissue-specific plasminogen activator in 15 patients. We observed that tenecteplase is effective in 14/15 (93.3%) of our patients, and none of them had any bleeding episodes.

1. Introduction

Parapneumonic pleural effusion occurs in approximately 35–60% of patients with pneumonia [1]. Conventional management practice of chest tube drainage and antimicrobial drugs in complicated parapneumonic effusion is effective in three-fourths of the cases [2]. Surgical management through pulmonary decortication was observed with an overall mortality of 3% and postoperative complications in 39% of the patients [3]. Pleural infections predispose to increased deposition of plasminogen activator inhibitors 1 and 2, thereby increasing the intrapleural fibrin deposition resulting in loculations [4]. Intrapleural thrombolytics facilitate pleural fluid drainage in complicated and loculated effusions by breaking up the loculations. A Cochrane review that included studies with streptokinase, urokinase, and alteplase concluded a significantly reduced mortality and requirement of surgical intervention [5]. Until date, there is only one preliminary report available with the use of tenecteplase as intrapleural thrombolytic agent [6]. Tenecteplase, like alteplase, is a recombinant tissue plasminogen activator selective to tissue plasminogen, thus expected with lower incidences of adverse events such as bleeding, following the systemic administration [7]. We wish to share our experience in using tenecteplase for facilitating the pleural fluid drainage in 15

patients with parapneumonic effusions in the present case series.

2. Case Series

We encountered 15 patients with parapneumonic effusion with the median (range) age of 43 (33–72) years and except for one; all the study participants were males. Written consent was obtained from each study participant. The baseline characteristics of the study participants are listed in Table 1. All the included patients had exudative polymorphic pleural fluid on aspiration. Most of the study participants had shown elevated total white blood cell count and C-reactive protein levels. Three participants were detected with loculated pleural effusion in ultrasonogram while seven by computed tomography. Twelve patients had pleural catheter, while three had chest tube for draining the pleural fluid.

3. Description of the Interventions

Following the confirmation of pleural effusion, ultrasound was carried out to identify the biggest pocket for inserting the catheter under ultrasound guidance and with local anesthesia. Special pleural catheter was prepared by keeping the stylet inside the catheter. After administration of local

TABLE 1: Key characteristics of the study participants.

| S. No. | Age; sex | Concomitant disorder | Baseline respiratory symptoms | Baseline total WBC count (count \times 10 ⁹ /L) | Baseline CRP (mg/L) | Aspirated pleural fluid glucose (mmol/L) | Aspirated pleural fluid WBC count (cells/ μ L) | Neutrophil percentage in the pleural fluid (%) | Number of loculations as detected in USG | Number of loculations as detected in CT |
|--------|----------|------------------------------------|-------------------------------|--|---------------------|--|--|--|--|---|
| 1 | 41; M | None | F, P, D | 11 | 305 | Not available | 790 | 82 | 2 | 3 |
| 2 | 54; M | Dyslipidemia | F, P, C, S | 8 | 161 | 6.9 | 7890 | 70 | 1 | 2 |
| 3 | 33; M | None | P, C, S | 16 | 241 | 6.8 | 1420 | 30 | 1 | 1 |
| 4 | 37; M | COVID-19 | F, P, D | 15 | 160 | Not available | 2100 | 50 | 1 | Not done |
| 5 | 37; M | None | F, P | 14 | Not available | 2.6 | 8740 | 79 | 1 | 1 |
| 6 | 34; M | None | F, P, D | 24 | 191 | 0.2 | 1306 | NA | 1 | 2 |
| 7 | 49; M | Diabetes | P | 13 | 160 | 7.3 | 830 | 87 | 1 | Not done |
| 8 | 72; M | Liver transplantation and CVA | C, S, D | 12 | Not available | Not available | 1610 | 80 | 1 | 2 |
| 9 | 40; Fe | None | F, P, D | 13 | Not available | 1.1 | 21780 | 84 | 1 | 1 |
| 10 | 41; M | G6PD deficiency | F, P, D | 11 | 180 | 0.2 | 2180 | 83 | 1 | 1 |
| 11 | 56; M | G6PD deficiency, diabetes | F, P, C, S, D | 8.8 | 291 | 3.9 | 890 | 89 | 2 | 3 |
| 12 | 48; M | Diabetes, systemic hypertension | P, C, D | 13.3 | 202 | 13.1 | 1580 | 65 | 1 | 2 |
| 13 | 68; M | Diabetes, IHD, atrial fibrillation | D | 14 | 206 | 7.7 | 2160 | 88 | 1 | 1 |
| 14 | 71; M | Dyslipidemia, CVA | F, P, C, S, D | 10 | Not available | 0.2 | 7210 | 90 | 1 | 1 |
| 15 | 64; M | None | D | 16 | Not available | 2.2 | 520 | 61 | 2 | 3 |

M: male; Fe: female; COVID-19: coronavirus 2019 infection; CVA: cerebrovascular accident; IHD: ischemic heart disease; F: fever; P: chest pain; C: cough; D: dyspnea; USG: ultrasonogram; CT: computed tomography.

TABLE 2: Details regarding the intervention (tenecteplase) and postinterventional events.

| S. No. | Frequency of tenecteplase application | Additional interventions needed for pleural drainage after tenecteplase | Chest X-ray picture following tenecteplase administration | Concomitant analgesics |
|--------|---------------------------------------|---|---|---------------------------|
| 1 | Four | None | Improved | Paracetamol and naproxen |
| 2 | Once | None | Clear | Paracetamol and ibuprofen |
| 3 | Once | None | Clear | None |
| 4 | Twice | None | Improved | None |
| 5 | Twice | None | Clear | Tramadol |
| 6 | Twice | Thoracotomy and decortication | No improvement | None |
| 7 | Twice | None | Clear | Tramadol |
| 8 | Twice | None | Clear | None |
| 9 | Twice | None | Clear | Tramadol |
| 10 | Twice | None | Clear | None |
| 11 | Once | None | Clear | Tramadol |
| 12 | Twice | None | Improved | Tramadol |
| 13 | Twice | None | Clear | Paracetamol |
| 14 | Once | None | Improved | None |
| 15 | Four | None | Clear | None |

anesthetics, the needle connected to a 20 cc syringe was inserted until the pleural fluid drained freely. Then, the syringe was disconnected, the guide wire was introduced, and after removing the needle, a space was created by blade to insert the dilator to open the tract for the catheter. After dilator removal, a catheter was introduced inside pleural cavity. As soon as the catheter was inside the pleural cavity, the stylet and guide wire were removed; catheter was opened and connected to a drainage box. Suction (ranging from 15 to 20 mmHg) was applied. Thoracic tube insertion was carried out in the traditional way.

Tenecteplase solution was prepared by keeping 3000 IU tenecteplase with 40 cc of 0.9 normal saline mixed 10 cc of 1% of lidocaine. The whole mixture was kept in a 50 mL syringe. The syringe was then connected to a 3-way lock catheter, and the solution was pushed inside the catheter followed by 20 mL normal saline flushing. The catheter was closed for one hour and then drained.

4. Details regarding Tenecteplase Administration and Postadministration Events

All the study participants were administered tenecteplase at 3000 IU. The key details of the intervention and postinterventional events are listed in Table 2. Following tenecteplase, all the participants had complete/near complete drainage of pleural fluid except one who needed additional thoracotomy with decortication for complete resolution. Ten (66.7%) had complete resolution of chest X-ray findings following the drainage after tenecteplase while four (26.7%) showed significant improvement from the baseline. Nearly half (8, 53.3%) required analgesics for pain control following the drainage. The administration of tenecteplase was considered to have failed when there was no improvement in the chest X-ray

or absence of any pleural fluid being drained or persistence of fever and/or chest pain. The interval time for evaluation and readministration of tenecteplase was 24 hours.

5. Discussion

We observed that tenecteplase is effective and safe in our patients with complicated parapneumonic effusion. The findings were like the only other report with tenecteplase where the authors have observed an efficacy rate of 92.1% (35/38 patients) and adverse events in only 6.9% (4/38) patients [6]. We observed the treatment failure rate of only one (out of the total 15) patient. Studies have reported around 27% failure rate with chest tube drainage alone [8]. Deoxyribonuclease (DNase) significantly decreases the viscosity of the pus in the pleural fluid and eases the drainage [9]. Intrapleural alteplase with DNase was observed to be successful in 58/61 (93.4%) of patients with bleeding in the pleural fluid requiring blood transfusion encountered in three (4.9%) patients [10]. Thrombolytics alone were observed with significantly lower success rate in large randomized clinical trials [11]. Tenecteplase with DNase is yet to be trialed, and it would be interesting and useful to evaluate the outcomes with this combination. Similarly, tenecteplase was observed to be effective even in our patients with 3 locules as detected by CT scan. Tenecteplase is a long-acting thrombolytic drug thus requiring fewer doses of administration for prolonged effect. We observed that except for two patients (due to partial response), the remaining required only one- or two-times administration. The prolonged duration of action of tenecteplase may be an advantage in patients with pleural effusion associated with inoperable lung cancer. We did not observe any bleeding episodes with tenecteplase despite two patients with the history of cerebrovascular accident. Fibrin-specific thrombolytic has been shown to be effective and safe even when used in patients

with thalassemia with baseline anaemia and on anticoagulation therapy [12]. The only side effect observed following intrapleural administration was pain at the local site that was effectively ameliorated in all the patients with analgesics. In fact, nearly half of our patients (8/15) did not require any analgesic as the pain was self-limiting.

6. Conclusion

We observed that intrapleural tenecteplase is effective and safe for facilitating drainage of pleural fluid in parapneumonic effusions. High quality randomized clinical trials with/without DNase combination are needed for confirming the therapeutic benefit of intrapleural tenecteplase.

Additional Points

Key Messages. (i) Intrapleural thrombolytics are effective in facilitating the drainage of complex pleural effusions. (ii) Previous studies have used streptokinase, urokinase, and alteplase. Only one published study is available encountering tenecteplase. (iii) We observed that tenecteplase is effective and safe in our patients with complicated parapneumonic pleural effusions.

Conflicts of Interest

The authors do not have any conflict of interest.

References

- [1] S. J. Chapman and R. J. Davies, "Recent advances in parapneumonic effusion and empyema," *Current Opinion in Pulmonary Medicine*, vol. 10, no. 4, pp. 299–304, 2004.
- [2] H. E. Davies, R. J. O. Davies, C. W. H. Davies, and on behalf of the BTS Pleural Disease Guideline Group, "Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010," *Thorax*, vol. 65, Suppl 2, pp. ii41–ii53, 2010.
- [3] C. W. Towe, S. R. Carr, J. M. Donahue et al., "Morbidity and 30-day mortality after decortication for parapneumonic empyema and pleural effusion among patients in the Society of Thoracic Surgeons' General Thoracic Surgery Database," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 157, no. 3, pp. 1288–1297.e4, 2019.
- [4] A. A. Komissarov, N. Rahman, Y. C. G. Lee et al., "Fibrin turnover and pleural organization: bench to bedside," *American Journal of Physiology. Lung Cellular and Molecular Physiology*, vol. 314, no. 5, pp. L757–L768, 2018.
- [5] E. S. Altmann, I. Crossingham, S. Wilson, and H. R. Davies, "Intra-pleural fibrinolytic therapy versus placebo, or a different fibrinolytic agent, in the treatment of adult parapneumonic effusions and empyema," *Cochrane Database of Systematic Reviews*, no. 10, article CD002312, 2019.
- [6] A. Refaat, N. Affara, T. Muhsen, and M. Salahuddin, "Intrapleural tenecteplase therapy in treatment of loculated parapneumonic pleural effusions and empyema," *Egyptian Journal of Chest Diseases and Tuberculosis*, vol. 63, no. 4, pp. 913–921, 2014.
- [7] S. B. Coutts, E. Berge, B. C. Campbell, K. W. Muir, and M. W. Parsons, "Tenecteplase for the treatment of acute ischemic stroke: a review of completed and ongoing randomized controlled trials," *International Journal of Stroke*, vol. 13, no. 9, pp. 885–892, 2018.
- [8] J. M. Porcel, "Chest tube drainage of the pleural space: a concise review for pulmonologists," *Tuberculosis and Respiratory Diseases*, vol. 81, no. 2, pp. 106–115, 2018.
- [9] F. Piccolo, N. Popowicz, D. Wong, and Y. C. Lee, "Intrapleural tissue plasminogen activator and deoxyribonuclease therapy for pleural infection," *Journal of Thoracic Disease*, vol. 7, no. 6, pp. 999–1008, 2015.
- [10] N. Popowicz, O. Bintcliffe, D. de Fonseca et al., "Dose de-escalation of intrapleural tissue plasminogen activator therapy for pleural infection. The alteplase dose assessment for pleural infection therapy project," *Annals of the American Thoracic Society*, vol. 14, no. 6, pp. 929–936, 2017.
- [11] N. A. Maskell, C. W. Davies, A. J. Nunn et al., "U.K. controlled trial of intrapleural streptokinase for pleural infection," *The New England Journal of Medicine*, vol. 352, no. 9, pp. 865–874, 2005.
- [12] X. K. Cheong, A. Yu-Lin Ban, and M. F. Abdul Hamid, "Short-course intrapleural alteplase and DNase in complex effusion with bleeding risk," *Respirology Case Reports*, vol. 8, no. 7, article e00648, 2020.