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Intrapleural Fibrinolysis in Post-tubercular Loculated Pleural Effusions at a Tertiary-Care Respiratory Center: An Uncontrolled Blinded Before-After Intervention Study

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Abstract

Background: Tuberculous, parapneumonic and traumatic loculated pleural-effusions pose therapeutic challenges due to resultant pleural-thickening and compromised lung-function for life. Tuberculosis is widely prevalent in developing countries, necessitating appropriate, effective, and economical treatment for loculated pleural-effusion to reduce the burden and sequelae.

Objective: An uncontrolled and blind before-after intervention study to determine the effectiveness of intrapleural fibrinolytic therapy (IPFT) using urokinase in loculated pleural effusions was conducted at a tertiary-care respiratory center after obtaining approval and written informed consent.

Methods: Fifty-one patients with loculated pleural effusion were administered with repeated cycles of three doses of 1 Lakh IU of urokinase intrapleurally until complete drainage of pleural fluid. Pre- and post-IPFT clinical and radiological responses were compared using removal of fluid, ultrasound, and chest radiography were compared. The Kolmogorov-Smirnov test and paired *t* test with significance at a *P* value less than 0.05 were applied to test statistically significant differences in proportions and means, respectively.

Results: Tuberculosis was the most common etiology leading to loculated pleural effusion (80%), and 82.4% of tuberculosis patients required at least two cycles of IPFT. Complete resolution in chest radiograph after IPFT was observed in 80.4% of patients. Chest pain (13.7%) and fever (9.8%) were the most common undesired effects associated with IPFT. A statistically significant reduction in mean intrapleural fluid levels pre- and post-IPFT from 184±81 ml to 67±52 ml was observed.

Conclusion: IPFT with urokinase is an effective treatment modality in patients with post-tubercular loculated pleural effusions. IPFT has minimal and tolerable undesired effects and prevents sequelae such as pleural thickening and consequent compromise of respiratory function.

Keywords: Tuberculosis, Intrapleural Fibrinolytic Therapy, Pleural Effusion, Urokinase

1. Background

Loculated pleural effusions usually occur as a result of adhesions and sequelae of complicated tuberculosis, parapneumonic effusion, empyema, haemothorax and malignant effusions.[1,2] The loculations result due to delay in initiating treatment, inappropriate use of antibiotics and long standing pleural effusion. Delayed hypersensitivity responses to *Mycobacterium tuberculosis* is implicated in the causation of pleural effusion in tuberculosis.[3-5] The presence of septae lead to formation of loculi resulting in poor drainage despite appropriately positioned patent intercostal tube, thereby increasing the susceptibility to device-associated secondary infections by emerging multidrug resistant organisms acquired in the hospital environment.[6-9] The consequential fibrosis of pleural cavity leads to pleural thickening and compromised pulmonary function, posing a therapeutic challenge for life.

Early and effective drainage of pleural effusion reduces

residual pleural thickening and helps in faster recovery of pulmonary function in patients with loculated pleural effusions.[10] Fibrinous locules in infected pleural cavity become a major hindrance for effective drainage of pleural effusion. Ultrasound guided catheter insertion and drainage is considered safe and effective procedure in pleural effusion, however the success rate is low when the effusion is loculated and septate.[11,12] Video assisted thoracic surgery (VATS) in loculated effusions is undoubtedly a better option, however it is both inaccessible and expensive option for vast majority of the population in resource limited facilities/communities. Open surgical modalities are more invasive and may be inaccessible or unaffordable by patients in developing countries.[13] Various agents used as fibrinolytics like streptokinase, urokinase and tissue Plasminogen Activator can be used intra-pleurally.[14,15]

Although there are existing controversies in the choice of fibrinolytic drug, 33 000 kDa low-molecular-weight urokinase is preferred over streptokinase due to rapid plasma half-life and ability to directly activate plasminogen to form plasmin.[16,17] In developing country set up, where tuberculosis is widely prevalent, it is essential to identify appropriate, effective and economical treatment modality for loculated pleural effusion so as to reduce the burden of its sequelae.

2. Objective

A pre-post intervention study to determine the effectiveness of intra-pleural fibrinolytic therapy (IPFT) using urokinase in patients with loculated pleural effusions was conducted at a tertiary-care respiratory centre after approval and written informed consent.

3. Methods

The present study was conducted as an uncontrolled, blinded, before-after intervention study in a 600-bedded Indian tertiary-care respiratory centre after approval by Institutional Ethics Committee and written informed consent of all patients. All 51 patients with persistent pleural fluid and poor chest-tube drainage despite an appropriately positioned and patent drain; multiple loculi or fibrin strands in pleura as depicted by ultrasonography or CT scan chest were included in the study. Patients who were less than 18 years of age, or having haemothorax, haemorrhagic pleural effusion, known sensitivity to urokinase, or any contraindications to thrombolytic therapy like haemorrhagic stroke, intracranial neoplasm, cranial surgery or head trauma within 14 days, major thoracic or abdominal surgery within ten days, and PT INR greater than 2 were excluded from the study.

On clinical suspicion of pleural effusion, chest radiography was done followed by ultrasonography for confirmation and quantification of fluid. Presence of loculations and marking of chest wall for site of insertion of chest drain was done with ultrasonographic assistance. Chest tube or pigtail thoracostomy catheter was inserted using strict aseptic precautions and fluid drained daily was noted. Patients with persistent fluid and poor tube drainage despite an ultrasonography-confirmed appropriately positioned and patent drain or multiple loculi or fibrin strands, depicted by ultrasonography or CT scan of chest, were included in the study for IPFT. Three doses of 100 000 IU of low molecular weight urokinase in 100 ml isotonic 0.9% sodium chloride solution were instilled in the chest tube at eight hours interval. Tube was clamped for 2 hours after instillation of each dose. Clinical response along with daily and cumulative drainage of pleural fluid was noted. X-ray and ultrasonography of chest was done after 48 hours after the instillation of last dose of urokinase. Patients with insignificant drainage and insignificant reduction in amount of fluid less than 50% radiologically were subjected to a repeat cycle of 3 doses. Chest tube was removed when both daily drainage of clear pleural fluid was less than 50 mL and ultrasonography chest showed presence of less than 50 mL of fluid in pleural cavity. Expansion of the lung was assessed radiologically by chest x-ray taken before and after the administration of urokinase. The reduction in the amount of pleural fluid by ultrasonography after IPFT was calculated. Spirometry was done after 48 hours of removal of chest tube. Pre and post-IPFT clinical and radiological response by removal of fluid, ultrasound, chest radiography and forced vital capacity were compared. The respiratory physician, sonologist, radiologist and spirometrist were blinded at all steps of the intervention study.

Data was entered and analyzed in IBM SPSS version 21.0. Means and proportions were calculated for continuous and categorical variables. Kolmogorov-Smirnov test was used for Normality test. A p value of less than 0.05 was considered statistically significant.

4. Results

Out of 51 patients, majority of the study participants (41.2%) were in the age group of 30–50 years, with an overall predominance of males (90.2%). Among all the study participants tuberculosis was the most common etiology (80.0%) leading to loculated pleural effusion followed by three cases of pneumonia with parapneumonic effusion and seven cases of malignant pleural effusion. Right-sided pleural effusion was more common (58.8%) than left-sided (35.3%). Three patients had bilateral pleural effusion and out of them two were more than 50 years of age (Table 1). All seven patients with malignant pleural effusion were more than 40 years of age including three females. There were four smokers. Five patients had primary carcinoma lung, one carcinoma breast with metastasis and another underwent diagnostic thoracoscopy to establish the diagnosis of malignant pleural effusion.

82.4% study participants required at least 2 cycles of IPFT before noticeable resolution in post-IPFT chest radiograph was observed in 80.4%. New onset undesired effects associated with IPFT included chest pain (13.7%) and fever (9.8%), however a vast majority of 76.4% of them did not report any. No bleeding was seen in any patient. Undesired effects did not require cessation of IPFT. No

Table 1. Clinico-demographic, Etiological, and Anatomical Profile (n = 51)

Characteristic	Number	Percent
Age (y)		
<30	19	37.3
30-50	21	41.2
>50	11	21.6
Gender		
Male	46	90.2
Female	5	9.8
Final diagnosis		
Tuberculosis	41	80.0
Pneumonia	3	14.0
Malignancy	7	6.0
Site of pleural effusion		
Right	30	58.8
Left	18	35.3
Bilateral	3	5.9

patients required more than three cycles of urokinase (Table 2).

Statistically significant differences in mean intra-pleural fluid present before and after IPFT from 184.51 ± 81.1 mL to 67.84 ± 52.1 mL was seen. Significant improvement in lung function post-IPFT was seen (Table 3).

The use of IPFT in malignant pleural effusion resulted in improvement of symptoms and helped prepare the patient for chemical pleurodesis which was attempted before ICD removal.

Table 2. IPFT With Urokinase: Intervention, Outcome, and Undesired Effect Profile (n=51)

Characteristic	Number	Percent
Number of IPFT Cycles		
1	24	47.1
2	18	35.3
3	9	17.6
Resolution in chest radiography after IPFT		
Yes	41	80.4
No	10	19.6
Undesired effects associated with IPFT		
Fever	5	9.8
Heart rate >100/min	2	3.9
Chest pain	7	13.7
Bleeding	0	0.0
None	39	76.4

Abbreviation: IPFT, Intrapleural fibrinolytic therapy.

5. Discussion

Treatment of loculated pleural effusion was always challenging, considering the controversies existing in the modalities of treatment and sequelae. The present study evaluated the effectiveness of urokinase as intra-pleural fibrinolytic agent in treatment of patients with loculated pleural effusion. These patients represent those individuals who usually do not respond to traditional modes of treatment for tubercular/parapneumonic/malignant pleural effusion. The use of intra-pleural fibrinolytics is a safer, easier and cost effective option and studies have shown it to be a useful alternative.[15-19] Pleural fluid present despite a radiologically confirmed correctly positioned intercostal drainage tube represents multiple locules in pleural cavity or tube obstruction due to increased viscosity of fluid. Fibrinous locules remain a major obstacle to effective drainage in an infected pleural cavity.[18-21]

IPFT with urokinase in loculated pleural effusion resulted in statistically significant reduction in the residual amount of fluid as noted by other researchers.[18] Systematic reviews and meta-analysis have proven intra-pleural urokinase in effectively reducing the need for surgery and reducing the duration of hospital stay, saving effort, costs, and reducing risks of healthcare associated infections.[22-24]

There is a dearth of studies on the use of urokinase for IPFT from developing countries despite its proven efficacy in the management of loculated pleural effusion from developed world. The present study establishes the effectiveness of urokinase as IPFT for loculated pleural effusion in a developing country set up. It prevents surgical decortication in large number of patients, an intervention associated with significant morbidity. IPFT has minimal and tolerable undesired effects and prevents sequelae such as pleural thickening and consequent compromise of respiratory function. It is easy to administer in a hospital set up and can be monitored by bedside ultrasonography. Morphological (hemorrhagic, serosanguinous, serous), cytological, biochemical (glucose and lactate dehydrogenase) and special (Interferon gamma and adenosine deaminase for tuberculosis) examination of aspirated pleural fluid may be required to differentiate various exudative pleural effusions. IPFT can also be administered in patients who have been subjected to

Table 3. Intrapleural Fluid Before and After IPFT (n=51)

Parameter	Mean	SD	Difference in Mean	95% CI of Difference in Mean	*P* Value
Fluid – Before IPFT	184.51	81.1	116.7	91.4-141.8	**<0.001**
Fluid – After IPFT	67.84	52.1			
In patients with tuberculous pleural effusion (n = 41)					
Fluid – Before IPFT	181.71	81.1	125.36	96.9-153.7	**<0.001**
Fluid – After IPFT	56.34	41.9			

Abbreviation: IPFT, Intrapleural fibrinolytic therapy.
Statistical test applied: Paired *t* test.

flushing with isotonic saline, placement of more catheters in loculi after ultrasound localization, thoracoscopic debridement and thoracotomy along with decortications, as IPFT does not require pre-conditioning.[25]

The possible limitations of the study include lack of control group of patients which was a consideration of the ethical issues. The intervention demonstrated improvement in pleural fluid drainage and lung function irrespective of the cause of effusion. The outcomes of the present study should be generalised with caution as the study population was not representative in terms of age and sex distribution. Being a single institutional experience of IPFT, infrastructural, logistic and procedural limitations need to be accounted for.[26]

6. Conclusion

IPFT with urokinase is an effective treatment modality in patients with post-tubercular loculated pleural effusions, preventing surgical decortications which is associated with significant morbidity. IPFT has minimal and tolerable undesired effects and prevents sequelae such as pleural thickening and consequent compromise of respiratory function.

Authors' Contributions

All authors contributed equally to the study.

Conflict of Interest Disclosures

None.

Ethical Approval

Ethical approval was covered by the Institutional Committee and informed consent was obtained from all patients.

Funding/Support

None.

Research Highlights

What Is Already Known?

Tuberculous, parapneumonic and traumatic loculated pleural effusions pose a therapeutic challenge due to the resultant pleural thickening and compromised lung function for life.

What This Study Adds?

IPFT with urokinase is an effective treatment modality in patients with post-tubercular loculated pleural effusions. IPFT has minimal and tolerable side effects and prevents sequelae such as pleural thickening and the consequent compromise of respiratory function.

References

1. Mason RJ, Broaddus VC, Martin TR, et al. Murray and Nadel's Textbook of Respiratory Medicine. Elsevier Health Sciences; 2010.
2. Idell S. The pathogenesis of pleural space loculation and fibrosis. Curr Opin Pulm Med. 2008;14(4):310-315. doi:10.1097/MCP.0b013e3282fd0d9b.
3. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CF. Tuberculous pleural effusions: advances and controversies. J Thorac Dis. 2015;7(6):981-991. doi:10.3978/j.issn.2072-1439.2015.02.18.
4. Light RW. Update on tuberculous pleural effusion. Respirology. 2010;15(3):451-458.doi:10.1111/j.1440-1843.2010.01723.x.
5. Sahni AK, Singh SP, Kumar A, Khan ID. Comparison of IS6110 and 'short fragment' devR (Rv3133c) gene targets with phenotypic methods for diagnosis of Mycobacterium tuberculosis. Med J Armed Forces India. 2013;69(4):341-344. doi:10.1016/j.mjafi.2013.02.003.
6. Khan ID, Sahni AK, Bharadwaj R, Lall M, Jindal AK, Sashindran VK. Emerging organisms in a tertiary healthcare set up. Med J Armed Forces India. 2014;70(2):120-128. doi:10.1016/j.mjafi.2013.09.005.
7. Khan ID, Lall M, Sen S, Ninawe SM, Chandola P. Multiresistant Elizabethkingia meningoseptica infections in tertiary care. Med J Armed Forces India. 2015;71(3):282-286. doi:10.1016/j.mjafi.2014.02.002.
8. Khan ID, Rajmohan KS, Gupta RM, et al. Invasive Cerebral and Pulmonary Mucormycosis in an Immunocompromised patient. J Basic Clin Med. 2017;6(2):9-11.
9. Khan ID, Basu A, Kiran S, Trivedi S, Pandit P, Chattoraj A. Device-Associated Healthcare-Associated Infections (DA-HAI) and the caveat of multiresistance in a multidisciplinary intensive care unit. Med J Armed Forces India. 2017;73(3):222-231. doi:10.1016/j.mjafi.2016.10.008.
10. Chung CL, Chen CH, Yeh CY, Sheu JR, Chang SC. Early effective drainage in the treatment of loculated tuberculous pleurisy. Eur Respir J. 2008;31(6):1261-1267. doi:10.1183/09031936.00122207.
11. Abusedera M, Alkady O. Ultrasound-guided Pleural Effusion Drainage With a Small Catheter Using the Single-step Trocar or Modified Seldinger Technique. J Bronchology Interv Pulmonol. 2016;23(2):138-145. doi:10.1097/lbr.0000000000000276.
12. Cantin L, Chartrand-Lefebvre C, Lepanto L, et al. Chest tube drainage under radiological guidance for pleural effusion and pneumothorax in a tertiary care university teaching hospital: Review of 51 cases. Can Respir J. 2005;12(1):29-33. doi:10.1155/2005/498709.
13. Khan ID, Sahni AK. Rapid Diagnosis of Dengue Outbreaks in Resource Limited Facilities. West Indian Med J. 2017;66(1):4-9. doi:10.7727/wimj.2016.095.
14. Sherry S, Johnson A, Tillett WS. The action of streptococcal desoxyribose nuclease (streptodornase)in vitro and on purulent pleural exudations of patients. J Clin Invest. 1949;28(5 Pt 2):1094-1104. doi:10.1172/jci102142.
15. Tillett WS, Sherry S, Read CT. The use of streptokinase-streptodornase in the treatment of postneumonic empyema. J Thorac Surg. 1951;21(3):275-297.
16. Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;352(9):865-874. doi:10.1056/NEJMoa042473.
17. Balfour-Lynn IM, Abrahamson E, Cohen G, et al. BTS guidelines for the management of pleural infection in children. Thorax. 2005;60 Suppl 1:i1-21. doi:10.1136/thx.2004.030676.
18. Cases Viedma E, Lorenzo Dus MJ, Gonzalez-Molina A, Sanchis Aldas JL. A study of loculated tuberculous pleural effusions treated with intrapleural urokinase. Respir Med. 2006;100(11):2037-2042. doi:10.1016/j.rmed.2006.02.010.
19. Janda S, Swiston J. Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyemas: a systematic review and meta-analysis. Chest. 2012;142(2):401-411. doi:10.1378/chest.11-3071.

20. Cameron R, Davies HR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema. Cochrane Database Syst Rev. 2008(2):Cd002312. doi:10.1002/14651858.CD002312.pub3.
21. Abu-Daff S, Maziak DE, Alshehab D, et al. Intrapleural fibrinolytic therapy (IPFT) in loculated pleural effusions--analysis of predictors for failure of therapy and bleeding: a cohort study. BMJ Open. 2013;3(2). doi:10.1136/bmjopen-2012-001887.
22. Janda S, Swiston J. Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyemas: a systematic review and meta-analysis. Chest. 2012;142(2):401-411. doi:10.1378/chest.11-3071.
23. Nie W, Liu Y, Ye J, et al. Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta-analysis of randomized control trials. Clin Respir J. 2014;8(3):281-291. doi:10.1111/crj.12068.
24. Khan ID, Gupta RM, Sen S, et al. Emerging Antimicrobial Resistance and Evolving Healthcare: Dangerous Crossroads for the Community and the Military. J Arch Mil Med. 2017;5(3):e12097. doi:10.5812/jamm.12097.
25. Barthwal MS, Marwah V, Chopra M, et al. A Five-Year Study of Intrapleural Fibrinolytic Therapy in Loculated Pleural Collections. Indian J Chest Dis Allied Sci. 2016;58(1):17-20.
26. Khan ID, Gupta N, Rangan NM, et al. Evaluation of Pre and Post Analytical Variables in Clinical Microbiology Services in Multidisciplinary ICU of a Medical College and Tertiary Care Hospital. J Basic Clin Med. 2016;5(1):2-4.