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Research Article

Two Intrapleural Fibrinolytics in Pleural Effusions; A Two Centres Retrospective Study

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2. Key words

Intrapleural fibrinolysis; Empyema; Thoracotomy

1. Abstract

1.1. Background: Fibrinolytics had been used for long in cases of empyema and loculated pleural effusions. They include streptokinase, urolkinase, tissue plasminogen activator and more recently dornase. We aimed at comparing streptokinase and tissue plasminogen activator as intrapleural fibrinoltyics in cases of empyema, encysted benign and malignant pleural effusions and retained clotted hemothorax.

1.2. Methods: We retrospectively reviewed our cases when we needed intrapleural fibrinolytics in King Abdullah Medical city; Makkah; Saudi Arabia and King Fahad Central hospital; Jizan; Saudi Arabia in the last 6 years between March 2012 and December 2018.

1.3. Results: We included 50 adult cases who needed intrapleural fibrinolytics. We used streptokinase 32(group 1) and used TPA in 18 cases (group 2). Age varied between16 and 87 years. Culture sensitivity, biochemical and cytology analysis of the aspirate was routinely performed in all. Chest tube was inserted in 34 cases and pigtails in 16. Empyema was diagnosed in 28. Loculated encysted pleural effusions were in 10 cases. Hemothorax was diagnosed in 6 and malignancy was confirmed or suspected in 6 cases. Group 1 had a significantly longer duration of chest drain after fibrinolysis, longer hospital stay, more readmissions, more need to decorticate either by VATS or thoracotomy. There was no significant difference in hospital mortality.

1.4. Conclusion: Intrapleural fibrinolysis is effective and safe and can save some surgical interventions. Tissue plasminogen activator is safer and better than streptokinase provided that the drain is functioning well.

3. Introduction and aim of the work

Empyema can be lethal in almost fifth of the cases. It has significant morbidity including restrictive lung diseases, cavitary pneumonia, Broncho pleural fistula, pneumothorax, lung abscess, empyema necessitans, trapped lung, septicemia, meningitis and shock[1, 2].Ultrasound following suspicious Chest-X- ray was recommended as the first-line option for imaging in suspected pleural effusion based on CXR. Computed tomography detects thickening, loculations, septations and measures the House field units of the collection suggesting its nature. Thoracocentesis and analysis of the fluid is the definitive diagnostic tool[1].

There are 3 stages of empyema according to the American thoracic society including the exudative, fibrinpurulent, and organizing stages. Complicated pleural effusions was diagnosed if pleural aspirate pH is < 7.20, glucose < 2.2 mmol/L, lactate dehydrogenase > 1000 IU/L, and positive Gram stain and/or bacte-rial culture. These criteria go with the well known little criteria. Empyema staging and localization of the pleural effusion is very important as treatment depends on the exact stage of the disease process[3-6].

As per the guidelines of the American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS), fibrino-

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lysis may be used in complicated effusions and frank empyema who do not improve after medical treatments and drainage[4-6].

It is to be noted that there is no indication for the routine use of intrapleural fibrinolytics in patients for pleural infection. There is no indication for the routine use of intrapleural fibrinolytics in patients for pleural infection. This statement is considered as Class (A) evidence[6, 7].

4. Patients and Methods

We reviewed the cases which needed intra-pleural fibrinolytics in 2 Centres in King Abdullah Medical City; Makkah and King Fahad Central hospital; Jizan; Saudi Arabia in the last 6 years be-tween March 2012 and December 2018. We included 50 adult patients admitted with empyema, loculated pleural effusion whether benign or malignant and retained clotted hemothorax who failed to improve clinically, laboratory and or radiologically after drainage and antibiotics. Routine history taking, physical examination and routine labs including biochemical, cytological and culture sensitivity of the pleural aspirate. Chest-X-ray, CT chest and US chest were performed. Empyema was suspected if the aspirate is thick, cloudy fluid With Fibrin present, smelly with leukocytosis, High lactic acid dehydrogenize level (> 3 normal values), Low pH (< 7.2) Glucose level < 60 mg/dl and or positive culture. Discussing the treatment plan with the family explaining the options of treatment, benefits and risk potentials is mandatory and informed written consent. Cephalosporin's whether 2nd or 3rd generations were empirically started unless a culture and sensitivity shows some different antibiotics requirement. We fol-low the temperature, WBCs and radiologic pictures of the patient. Chest tubes and or pigtails were inserted either by an interventional radiologist or thoracic surgeons preferably image guided for proper localization of the collections. We usually insert at least 32 French chest tubes or 10-12 French pigtail connected to underwater seal and not urine collection bags. We usually con-nect the drain to −20

cm H_2O of continuous suction and flushes with 10 ml normal saline and milking of the drain to get the best possible function. Group 1 received intra-pleural 25000 IU of streptokinase in 50 ml saline daily for 3 days. Group 2 received intra-pleural TPA 10 mgm in 50 ml normal saline. The drain was clamped for 3 hours and then opened. The patient is instructed to lie in different positions to assure as homogenous distribution of the fibrinolytic substance as possible. The pleural drain is removed once drainage decreases to less than 100 ml/day for 2 days with clinical, lab and radiological improvement. The patients who showed clinical, laboratory and > 50% radiological improvement were discharged home one day after chest tube removal and were followed up by the chest surgeon or the chest physician in A WEEK TIME AND THEN ON A 3 MONTHS INTERVAL UNLESS THERE IS A SIGNIFICANT COMPLAINT when they will follow with the pulmonologist. Those who failed to improve are offered surgery whether VATS and or thoracotomy for decortications, biopsying and drainage of the collection. Those VATS who showed extensive adhesions and multiple pockets or those who cannot tolerate single lung ventilation were offered thoracotomy. We reviewed the files of those patients retrospectively. We collected the available data in the files. Patients were followed in the out patients clinic by both pulmonologists and or thoracic surgeons. P value was considered significant if less than 0.05

5. Result

Group 1 included 32 cases and group 2 included 18 cases. The commonest indication was empyema in 56% followed by loculated effusion, hemothorax and malignant pleural effusions **(Table 1)**.

The median age was 31 years. Females were more in our study. Chest tube was inserted in 34 cases (68%). Pigtails were inserted in 32%. The function of the drain was better in group 2 depend-ing upon the amount of drainage daily and oscillation of the fluid in the tubing system at rest, deep breath, and deep cough and on suction. The amount and duration of the pre fibrinolysis drain-age, WBCs and antibiotics intake was more or less equal(120 ml/ day for 12 days and 130 ml/day for 13days), 14000/dl,13000/dl and 93% and 89% respectively. Side effects were more in group 1 including severe pain requiring tramadol and or allergy requiring corticosteroids (**Table 2**).

We excluded any proved TB cases. Malignancy was suspected or confirmed in 6 cases whether 1ry or 2ry. Chronic renal failure was the predisposing factor in 8 cases in both groups (5 in group 1 and 3 in **group 2**). Diabetes Mellitus was uncontrolled in 11 cases (8 in **group 1** and 3 in **group 2**). Follow up was complete and available in 30 cases 60%. The median follow up was 21 months.

Table 1: Indications of intra-pleural fibrinolysis.

	Group 1	Group 2
No.	32	18
Empyema	18	10
Loculated Effusion	6	4
Hemothorax	4	2
Malignant	4	2

Table 2: Results of the 2 groups.

Median Age	33	29
Chest tube	27(68%)	7(39%)
Pigtail	5(32%)	11(61%)
Function of the drain	good	Excellent
Amount before fibrinolysis	120ml/day	130ml/day
Duration of symptoms before	16 days	15 days
WBCs	14000	13000
Antibiotics	26(93%)	16(89%)
Side effects ; pain, allergy	3(11%)	1(5.6%)
Duration of drainage after fibrinolysis	6 days	5 days
Amount of drainage after 3 days of fibrinolysis	230ml/day(20.40.170.270.380.500)	300ml/ day(30.70.200.550.650)
VATS	8(29%)	2(11%)
Thoracotomy	4(14.5%)	0
Mortality	2(7.2%)	1(5.6%)
Readmission	3(10.7%)	1(5.6%)

6. Discussion

Antibiotics alone may not be sufficient in complex pleural effusions. So, drainage by either aspiration, chest tube or pigtail is a must in such cases with or without intrapleural fibrinolysis[8]. The gold standard in the past was surgery whether VATS or decortications [5].

Our protocol is to use intrapleural fibrinolysis in cases of failed cases of encystedpleural collections and or empyema which failed to improve after drainage and antibiotics. We consent our patients after explaining the options of treatment and risk potentials. We give 3 consecutive daily doses of the fibrinolytics only. We clamp the drain for 3 hours and then open it. We ask the patients to get different positions for 30 minutes each to get a homogenous distribution of the fibrinolytics in the pleura as possible as it can be. Streptokinase 250 000 units was given in 50 ml normal saline. Alteplase tissue plasminogen activator 10 mgm was given in 50 ml normal saline. This is similar to those in Rahman NM et al[9]. In the study of Abu-Daff etal.[9], they used to inject 16 mg of t-PA and or 250 000 IU of streptokinase after diluting them in 100 cc of normal saline. They then give them intrapleurally through the chest drain once daily for 3 days. They clamp the drain for only 2 hours and they preferred to use a small drain 8-14 F US guided. Another course of intrapleural fibrinolytics were given if still needed[10, 11]. Taylor R F H, et.al. 1994 described 2 -6 doses used over 2 -35 days[12].

Light et. 2000 found 10 mgm of TPA the best dose to be used.

There is no worldwide consensus about the best protocol of fibrinolysis yet and some centres are using the 2 fibrinolytics together[13, 1]. Streptokinase and urokinase are the first genera-tion fibrinolytics used to treat empyema and loculated effusions. Urokinase has a direct action while streptokinase has an indirect fibrinolytic action. Tissue plasminogen activator has a direct ac-tion with little or no allergic complications with a 5 minutes half life. Fibrinolytics breaker the adhesions, loculations and help the drainage of the pleura [1-14]. Our retrospective study included 50 adults diagnosed as empyema in 56% followed by loculated effusion, hemothorax and malignant pleural effusions with a drain which did not solve the problem with still clinical and or radiological evidence of complicated empyema and or encysted effusions. Abu-Daff etal.[11] used them for the same indications but in different rates(74%, 10%, 14% and 4%) for empyemas, loculated effusions, hemothorax and other undefined pathologies[10]. We used chest tubes in 68% of our cases while Abu-Daff etal. [12], used them in only in about 32% of the cases. Their preference was to use radio logically guided pigtails emphasizing the importance of better localization and function of the drain rather than the size[10]. Side effects were more in group 1(11%) almost double those in group 2. They included significant chest pain after injection which mandated the use of tramadol or severe allergy requiring corticosteroids. But none of these never obliged us to stop the intra-pleural fibrinolysis. We fortunately never had bleeding in our series. Abu-Daff etal. [10]Reported complica-tions in 25% of his series including 6.6% with significant bleeding requiring blood transfusion in 3.35 and or urgent thoracotomy in 3 cases to control bleeding and one patient needed angio embolization of the bleeding internal mammary artery. As they had more cases of hemothorax in their series; about 10% [10].

The efficacy in our study is governed by the duration and amount of drainage after injection, radiological improvement, and clini-cal improvement including the temp.

WBCs, CRP, general condition need VATS thoracotomy, readmissions for complications such as septicemia, shock, fistula, abscess or significant pneumonia. These parameters follow those of many studies before such as[1, 2, 5, 6, 8, 9] Alteplase led to a better and quicker drainage in the drain 300ml/day VS 200ml/ day and 5 VS 6 days, less need to get intervention(11% VS 25%) whether VATS or thoracotomy which were both for decortica-tion and drainage and none for bleeding. Group 2 had an earlier discharge home, less readmissions for septic complications(5.6% VS 10.7%) and less mortality (5.6% VS 7.2%). The better results of TPA over streptokinase in our series may be either due to its nature or may be due to better localization of the target by US evidenced by better function of the drain and more amount of

pre injection drainage. Subgroup analysis was done for the cases of US guided localization of the collection gave almost the same results proving more efficacy and better safety of the TPA. While Maskell et al. [12] found no significant benefit for streptokinase in empyema or complicated pleural effusions in MIST Trial 1[15]. Cameron RJ and Davies H. 2009 found a significant reduction in requiring surgical interventions without increased side effects. The Cochrane review concluded that intrapleural fibrinolytics cannot be recommended as the standard treatment of parapneumonic effusion and empyema but can be beneficial after failure of drainage and antibiotiocs[16].

MIST 2 Trial found improvement with only Intrapleural t-PA-DNase therapy but not with either DNase alone or t-PA alone[11].

We recently started our VATS program, so our experience is still limited and we are trying to improve our learning curve. That is why all our cases that failed fibrinolysis had VATS; 10 cases. Half of them we felt that we cannot complete a good job with VATS only so, we did thoracotomy. We had 3 hospital mortalities. All of them was not related to the fibrinolysis. One of them had Non Hodking Lymphoma and finished her chemotherapy 2 months ago. She had generalized septicemia and positive cultures in urine and central lines. The 2nd patient had uraemic cardiomyopathy, heart failure and uncontrolled arrhythmias postoperatively. The 3rd patient had suuden death in the 11th postoperative day mostly due to pulmonary embolism.

7. Conclusion

Intrapleural fibrinolysis is effective and safe and can save some surgical interventions. Tissue plasminogen activator is safer and better than streptokinase provided that the drain is functioning well.

8. Limitations of the Study

This is a retrospective study having the inherent deficiencies of the retrospective studies. The number of cases is relatively small with different aetiologies. More follow up may be needed.

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