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ORIGINAL ARTICLE

Evolving Fibrinolytic Option in the Management of Second Stage of Empyema

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ABSTRACT

Background: Intrapleural fibrinolytics installation is considered an alternative method to aggressive operative intervention. This conservative medical management may decrease morbidity and mortality that were recorded with surgery. Our study investigates the outcome of tissue plasminogen activator (TPA), alteplase, and streptokinase (SK) as a treatment for stage II of empyema.

Methods: This study prospectively evaluated 38 patients that had stage II of empyema. The patients were divided into two groups with installing one fibrinolytic protocol into a chest tube for each group: group A, (TPA) and group B, (SK). The evaluation was based upon clinical examination and radiological findings for the efficacy of each protocol.

Results: There were no differences in baseline characteristics between both groups. There was a significant improvement after 1st, where 11 patients (52.4%) improved in the TPA group with only 3 patients (17.6%) in the SK group. TPA group showed 100% success, on the other hand, SK Group had 2 patients' failure (11.8%) and surgical intervention was necessary for them. Hemorrhagic complications were 9.5% and 17.6% for TPA and SK respectively. Finally, there was a significantly prolonged duration of mean hospital stay with SK therapy (5.48 vs 8.59 days).

Conclusions: Both fibrinolytic protocols were effective and safe for empyema management, but Alteplase had a better outcome**.**

Keywords: Empyema; Fibrinolytic therapy; Intra-pleural installation; Tissue plasminogen activator; Streptokinase

INTRODUCTION

Empyema is a condition of frank pus with or without multiple loculations. The management of empyema is always by intercostal chest tube (ICT) drainage with or without fibrinolytics or by surgical drainage. Treatment of early cases of empyema is a challenge in the thoracic surgery field as it can exclude the surgery and its complications [1].

The treatment of choice for pleural space collections is pleural drainage. Evacuation alone with simple closed thoracostomy, adequate management of chest tube, and antibiotics when indicated are often enough in the early stages. In late stages, decortication is usually performed. Fibrinolytics installation into the pleural cavity has been used with favorable outcomes and approved as an alternative to surgical interventions [2].

The American thoracic society had classified empyema as stage I (exudative stage), stage II (fibrinopurulent stage), and stage III (organizing stage). Simple closed chest drainage plus the antibiotics can control Stage I with a success rate of about 80%, but in stages II and III, the antibiotics and closed drainage are not much effective [3].

The fibrinolytic protocols, that are considered conservative medical treatment, along with tube thoracostomy are an effective management for fibrinopurulent empyema, and may be to some extent for organized empyema, may reduce morbidity, and may have a low medical [4].

Tissue plasminogen activator (TPA), Alteplase, was initiated to replace streptokinase and urokinase. TPA has an improved ability to bind directly to fibrin compared with the older fibrinolytics. TPA is the most important physiologic plasminogen activator in the blood [5]. Streptokinase (SK) is a non-enzymatic protein that indirectly activates the fibrinolytic system. Streptokinase forms a complex that can cleave other plasminogen molecules forming plasmin [6].

In this study, we evaluated the safety and efficacy of TPA and SK as a fibrinolytic therapy in the management of 2nd stage of empyema.

METHODS

This non-randomized prospective study was conducted in Zagazig university hospitals between May 2019 to August 2021, where 42 patients were represented with complicated pleural effusion. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Full history and physical examination were reviewed for all patients before starting the protocol. Then routine laboratory investigations, chest imaging, and pleural fluid analysis were done to document that all patients were in stage II.

Inclusion criteria included clinically infected pleural effusion that was requiring drainage and had fibropurulent nature with or without positive gram stain fluid in addition to pleural fluid analysis which had the criteria of stage II empyema with an acidic pH below 7.2, glucose below 40 mg, and lactate dehydrogenase (LDH) more than 500 IU. Informed consent was fixed for all patients before starting the study.

Exclusion criteria included patients aged < 16 years, pregnant or lactating females, patients who had hepatic failure or known sensitivity to SK or TPA, pleural fluid analysis which revealed glucose > 40 mg, LDH > 500 IU, and pH > 7.2, and expected survival less than two months (as metastatic carcinoma and coincidental stroke). The criteria also included patients who previously received intra-pleural fibrinolytics, major surgery in the previous 7 days, previous pneumonectomy, or suspected bronchopleural fistula on the side of infection, and patients on anticoagulant or antiplatelet therapy.

Four patients who were noted in the exudative phase (glucose > 40 mg, LDH > 500 IU, PH > 7.2) with serous pleural effusion were excluded from the study.

Thirty-eight patients, who were selected as the fibropurulent phase, were divided into two groups with applying one fibrinolytic protocol in each group as follows:

Group A, TPA: 21 patients were enrolled, where 10 mg of TPA were diluted in 50 ml normal saline solution (NSS) and installed through (ICT).

Group B, SK: 17 patients were enrolled, where 2500 units of SK were diluted in 50 ml NSS and installed through ICT.

After installation of each fibrinolytic, 30 ml NSS was pushed to wash all fibrinolytic amount into pleural space and the ICT was clamped for 6 hours then the clamp was released to allow the drainage. Chest physiotherapy plus decubitus change regimen were applied to all patients to ensure fair distribution of fibrinolytics.

The protocol was repeated daily for 3 successive days as needed depending on opacity resolution, where the patients were evaluated by daily chest x-ray (CXR). Also, ICT drainage was evaluated daily for the amount and the character. We followed the method of Brockelsby and associates to estimate pleural collection amount by counting intercostal space (ICS) starting from costophrenic angle as follows: 1 ICS= small - localized collection, 2–3 ICS= medium collection, large collection if ≥ 4 ICS [7].

At the end of the course, computed tomography (CT) was done. According to the study of Moy and colleagues, the pleural collection amount was classified on CT with a three-point scale as follows: small, moderate, and large sizes based on the anteroposterior (AP) quartile and maximum AP depth [8].

Hemorrhagic complications were noted such as the drop in hemoglobin and hematocrit, blood transfusion, hemorrhagic drainage from ICT, epistaxis, hemoptysis, and bleeding from the site of ICT.

Protocol failure was defined as the need for further management as thoracotomy or thoracoscopy. Protocol success was defined as opacity resolution on chest imaging with no need for further management. The hospital stay was recorded as the time between empyema diagnosis and discharge or death.

Statistical analysis:

All analyses were performed using SPSS software version 22 (USA). Descriptive statistics were used to summarize the patients' data. The t-test was used to examine differences between groups with parametric data. Fisher's exact test was used for categorical variables. A "P" value of 0.05 or less was considered statistically significant.

RESULTS

Detailed baseline characteristics are presented in table (1), with no significant difference between both groups. The mean age of group A was 39.7 years, while in group B it was 38.8 years. Male patients were 16 (76.2%) and 10 (58.8%) for group A and group B respectively. Smoking, diabetes, and ischemic heart disease (IHD) were the most common pathologies. 52.4% of group A patients had right side empyema and 47.6% had left side empyema, while 70.6% of group B had right side empyema and 29.4% had left side empyema. 81% of group A patients had positive fluid culture versus 70.6% for group B. The manifestations duration before starting the management was about the same for both groups.

The outcome of the different variables is listed in table (2). Complete resolution of empyema after 1st dose was achieved in 11 patients (52.4%) from group A and in 3 patients only (17.6%) from group B. This dramatic improvement, which is considered a success, was statistically significant in favor of TPA.

In group A, 9 patients (42.9%) improved after the 2nd dose and the last patient (4.7%) in this group exhibited full drainage of empyema after the 3rd dose of TPA. In group B, 6 patients (35.3 %) improved after the 2nd dose. After the 3rd dose, 8 patients (47.06%) in group B showed empyema improvement but 2 of them were still suffering from minimal pleural collection necessitating follow-up for drainage via the ICT for 2 more days. These two patients were still representing just obliteration of costophrenic angles after the 2 days and so the ICT was removed and we conserved them in the outpatient clinic for 1 month, by the end of the follow-up period the opacity was almost disappeared. No significant differences were recorded after the 2nd and 3rd doses regarding empyema resolution between both groups. The SK protocol failed in the remaining 2 patients (11.8%) of group B, where they showed moderate to large collection and were shifted for operative drainage and decortication by video-assisted thoracoscopy (VATS). TPA protocol showed no case failure with no significant difference between both protocols regarding the failure.

There was no significant difference regarding hemorrhagic complications between both groups. Two patients (9.5%) in group A suffered from blood-tinged sputum and bleeding from the ICT site. Three patients (17.6%) in group B suffered from epistaxis and blood-tinged sputum. All patients with hemorrhagic complications in both groups were managed conservatively without any specific therapy or blood transfusion.

The mean duration of hospital stay was significantly prolonged in the SK group, it was 8.59 ± 3.30 days versus 5.48 ± 1.69 days for the TPA group with a significant P-value of 0.001.

Table 1: Baseline characteristics of the patients in both groups.

Variables	Group A (n=21)	Group B (n=17)	P-value
Age, years (range)	39.7 ± 9.8 (23-59)	38.8 ± 9.3 (24-54)	0.196
Sex, n (%) • Male • female	16 (76.2%) 5 (23.8%)	10 (58.8%) 7 (41.2%)	0.307
Comorbidities, n (%) • Smoking • Diabetes • IHD	14 (66.7%) 10 (47.6%) 4 (19%)	9 (52.9%) 10 (58.8%) 2 (11.8%)	0.509 0.532 0.672
Empyema side, n (%) • Right • Left	11 (52.4%) 10 (47.6%)	12 (70.6%) 5 (29.4%)	0.748
Positive fluid culture, n (%)	17 (81%)	12 (70.6%)	0.703
Manifestation duration, days	14.83 ± 1.04	13.75 ± 1.02	0.662

Table 2: Outcomes of the variables

Variables	Group A (n=21)	Group B (n=17)	P-value
Improvement after the 1st dose, n (%)	11 (52.4%)	3 (17.6%)	0.043*
Failure after the full course, n (%)	0 (0%)	2 (11.8%)	0.193
Hemorrhagic complications, n (%)	2 (9.5%)	3 (17.6%)	0.640
Mean hospital stay, days (range)	5.48 ± 1.69 (4-11)	8.59 ± 3.30 (4-16)	0.001*

* = significant.

DISCUSSION

The first successful trial for the use of fibrinolytics installation as management for empyema was done in 1949 by Sherry and associates [9]. British Thoracic Society has recommended the fibrinolytics therapy for empyema [10]. Many studies followed this point, however, most of them discussed urokinase (UK) and SK with equal efficacy, and only few studies had measured the use of TPA despite its increased use in the management of empyema [11].

So, our study evaluated the outcome of TPA and SK use for the management of empyema in stage II. A limited number of patients in this study was examined due to the economic consideration for fibrinolytics, especially when compared to operative intervention by thoracotomy or even by VATS plus unhidden risks and expenses of fibrinolytics.

Our study showed successful and safe use of intrapleural installation of fibrinolytics, TPA, and SK in the management of empyema. However, the TPA protocol showed a higher success rate than the SK protocol, where after the full course of both protocols, the empyema clearness rates were 100% and 88.2% for TPA and SK respectively. Also, this TPA success rate was significantly higher than SK after the 1st dose.

Ben-Or and his colleagues observed in their study similar results to our study [12]. Intra-pleural installation of TPA was successful in 78.1% (25 of 32 patients) of patients with empyema. Thommi and associates showed a congruent result [13]. TPA installation into the pleural cavity should be considered in the initial management of complicated pleural effusions and empyema that fail to resolute by ICT drainage.

Israel and Blackmer showed a compatible study with us [14]. They evaluated all randomized controlled trials of intrapleural installation of TPA for treatment of empyema in the pediatric patients through ICT. They found that intrapleural TPA has a powerful effect in the treatment of parapneumonic effusions and on empyema resolution. Barthwal and his colleagues carried out a five-year retrospective observational study of 200 patients with loculated pleural collections and failed tube drainage and managed with fibrinolytics: SK and UK [15]. They had favorable results when they used both of them, SK/UK, with success rates of 83% and 60.8% in complicated pleural effusion and empyema respectively, with equivalent responses to either agent.

On contrary, Rahman and co-workers conducted a blinded, 2-by-2 factorial trial in which 210 patients with pleural infection were randomly assigned to receive one of four study treatments for 3 days: double placebo, TPA, and DNase, TPA and placebo, or DNase and placebo [16]. Intrapleural installation of TPA–DNase combination has a great effect in improving fluid drainage in patients with pleural infection and decreasing the surgical need and hospital stay duration. TPA alone or DNase alone was ineffective in managing empyema. Samancilar and his colleagues found that intrapleural fibrinolytic therapy has no extra benefit in the management of complicated pleural effusion or empyema [16].

Increased hemorrhagic complications after intrapleural installation of fibrinolytics is considered one of the most important challenges in thoracic surgery. In our study, we reported excellent safe outcome regarding the risk of bleeding. Only two patients (9.5%) in the TPA protocol suffered from blood-tinged sputum and three patients (17.6%) in

the SK protocol suffered from blood-tinged sputum and epistaxis. All bleeding complications in both groups were managed conservatively.

Our result goes with the study of Shirota and Uchida [18]. They reported effective safe outcome regarding treatment-related complications. Thommi and co-workers, who evaluated 120 patients, recorded a 2% rate of bleeding from the ICT site and blood was transfused for one patient [13].

In our study, the mean hospital stay was significantly prolonged in the SK group (8.59 days) than in the TPA group (5.48 days) with a P-value of 0.001. The prolonged hospital stay for the SK group was mostly related to 4 cases that showed a residual pleural collection of different grades. Two of them had a minimal pleural collection necessitating 2 more days' observation for ICT drainage. The other 2 patients had more than moderate pleural collection, and SK protocol failure and they underwent operative intervention for drainage and decortication by VATS.

Kheir and associates, who conducted a prospective multicenter, randomized controlled trial involving 32 patients who underwent SK therapy for pleural infection, reported a similar result to our study [19]. SK protocol showed longer mean hospital stay up to 6 days. Ekingen and co-workers observed a more similar result of significantly prolonged hospital stay with the use of SK therapy, they recorded a mean hospital stay of up to 22.4 days [20].

In fact, other than thoracotomy, VATS is believed to be the best available modality for empyema with success rates between 85% and 98% [21]. Also, a decision to proceed to open thoracotomy can be easily made upon the VATS sitting. However, VATS may be not routinely available in many centers. Many series advocated that VATS application is the 1st choice in the management of empyema, in which ICT remains insufficient, with a high success rate and considerably decrease the need for open drainage by thoracotomy [21,22].

On contrary, Zuckerman and co-workers conducted a randomized prospective study on 25 patients and demonstrated that the intrapleural installation of TPA was effective in loculated complicated para-pneumonic effusion and empyema and can be performed safely in some patients to avoid the need for surgical intervention [23]. Another study by Shirota and Uchida reported that the fibrinolytics to be administered in complicated para-pneumonic effusion and empyema were 95% effective, well tolerated, and to be applied as the first line of treatment [18]. These results support the efficacy of fibrinolytic therapy that deserves more attention before proceeding to VATS and general anesthesia with their known risks and limitations.

CONCLUSION

The optimal management of complicated pleural effusion and empyema is still under debate, with the management ranging from ICT alone to fibrinolytics installation to VATS/thoracotomy. However, this study suggests that administration of both fibrinolytic protocols, TPA and SK, for empyema management was safe and successful, but TPA had a better outcome with dramatic empyema management and shorter duration of hospital stay without failure. Alteplase installation is a valid and simple option that can be used before the shift to operative intervention and general anesthesia with their known risks. Multicenter trials with larger numbers of patients will help more to confirm the best managing protocol for empyema.

Conflict of Interest: None

Financial Disclosures: None

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