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ORIGINAL ARTICLE

Outcomes of two different chemical modalities in management of post traumatic clotted hemothorax.

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ABSTRACT

Background: Management of traumatic hemothorax is an important problem in thoracic surgery. As an alternative to surgical treatment in patients who developed clotted hemothorax after trauma, intra-pleural fibrinolysis has been used with favorable results. This modality of treatment may reduce known morbidities secondary to surgical procedures and may result in significant medical cost savings. Aim of the study is to test the efficacy and safety of tissue plasminogen activator and Streptokinase for management of post traumatic clotted hemothorax.

METHODS: our study included 40 patients presented with clotted hemothorax after chest trauma. Patients were divided into two groups each contains 20 patients. First group treated with intra-pleural Alteplase (tissue plasminogen activator) and the second group treated with streptokinase, both was instilled via an intercostal chest tube. Clinical and radiologic (chest radiographs (CXR) and chest computed tomography (CT) data used for evaluation of efficacy of both protocols.

RESULTS: Alteplase give excellent results in clotted hemothorax, it showed dramatic improvement in both chest tube drain and pleural thickness without bleeding complications. Streptokinase protocol showed only improvement of chest tube drain.

CONCLUSIONS: Intra pleural Alteplase is safe and more efficient than Streptokinase as a chemical modality in treating patients presented with post traumatic clotted hemothorax.

KEYWORDS: Clotted; Hemothorax; Trauma; Alteplase; Streptokinase.

INTRODUCTION

Hemothorax is mostly a result of thoracic trauma either blunt or penetrating. Although tube thoracostomy is commonly adequate for the management of a hemothorax in most instances, failure of full drainage with tube thoracostomy and development of clotted hemothorax may occur in 5% to 30% of cases [1]. When clotted hemothorax developed tube thoracostomy drainage alone became ineffective. Insufficient drainage carries a number of well-known problems in posttraumatic clotted hemothorax [2]. A second chest tube is usually an inadequate alternative in retained clotted hemothorax where initial tube thoracostomy was insufficient. Controversy still exists regarding the approach to management of residual clotted hemothorax after chest trauma. Both aggressive and conservative types of treatment of clotted hemothorax had been advocated [3]. Intrapleural administration of fibrinolyic agents such as streptokinase, urokinase and tissue plasminogen activator (TPA) were suggested as a possible option for management of traumatic retained hemothorax. Streptokinase (SK) is a non-enzymatic protein that indirectly activates the fibrinolytic system [4]. SK forms a complex with plasminogen. This complex is able to act as a protease and cleave other plasminogen molecules, resulting in the formation of plasmin [5]. Tissue plasminogen activator (TPA), also known as Alteplase, was developed to replace streptokinase and urokinase (UK) Tissue plasminogen activator has an improved ability to bind directly to fibrin compared with the older fibrinolytics [6]. It is the most important physiologic plasminogen activator in the blood. Plasmin is generated when t-PA and plasminogen bind to fibrin [7].Plasmin is ultimately breaks down the fibrin threads inside the blood clots and surrounding adhesions, thus facilitates dissolution and drainage of the retained traumatic hemothorax [2] The aim of the present study was to test the safety and efficacy of tissue plasminogen activator (TPA) and Streptokinase

(SK) for management of post traumatic clotted hemothorax.

METHODS

Our comparative study included 40 patients collected in a nonrandomized fashion. All patients were admitted and operated in cardiothoracic surgery department – Zagazig University hospitals – Egypt, and in King Khalid hospital –Najran, Saudi Arabia from January 2018 to January 2020. They were divided into two groups each group contains 20 patients, one fibrinolytic protocol used for each group. Research ethical committee of cardiothoracic surgery department, Faculty of Medicine, Zagazig University) has given approval for the study. Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: patients who presented with clotted hemothorax after thoracic trauma documented with CXR and CT chest examination that showed residual opacity after initial drainage of hemothorax Inspite of properly positioned and well-functioning chest tube.

Exclusion criteria: Patients who had associated head trauma, cerebral hemorrhage or had recent stroke. Patients who had major surgery (e.g. abdominal exploration). Patients who suffered from severe lung injury (big lung contusion) or bronchopleural fistula suspected by prolonged air leak. Pregnant or lactating female. patients on oral anticoagulation therapy (e.g. cardiac valve replacement) or injection anticoagulation (heparin /Enoxaparin). Patients on antiplatelet treatment (e.g. Aspirin/clopidogrel in ischemic heart disease, coronary stents). Patients who had hepatic failure or known sensitivity to SK or tissue plasminogen activator. **Preoperative measures:** Before starting fibrinolytic treatment protocols, history and physical examination reviewed for each patient, routine laboratory investigations were done with special attention to complete blood count and the coagulation profile. Radiological investigations included CXR and chest CT.

Failure of treatment protocols: defined as the need for further intervention (VATS, thoracotomy). Success was defined as improvement in chest radiographs with resolution of previous pleural opacity.

Bleeding complications: were recorded if occurred such as hemoptysis, bleeding per nose, increased sanguineous drainage from tube thoracostomy, a decrease in Hb% & Hematocrit, need for blood transfusion after administration of Intrapleural fibrinolyic therapy.

Protocols for fibrinolytic agent's administration:

Group I (Intrapleural Alteplase protocol):

The protocol was conducted on 20 patients who had clotted hemothorax. Alteplase (Actilyse vials (Tissue Plasminogen Activator), Boehringer Ingelheim Co.) Administered as 10 mg diluted in 50 ml of normal saline instilled via the chest tube, then the chest tube washed by 30 ml normal saline to ensure that all Alteplase (TPA) delivered inside the pleural cavity.

Group II (Intrapleural streptokinase protocol):

The protocol was conducted on 20 patients. Streptokinase 250,000 units diluted in 50 ml of normal saline instilled via the chest tube, followed by wash of the chest tube by 30 ml normal saline to ensure streptokinase delivered inside pleural cavity. Then**,** chest tubes of all patients in both groups were clamped for 6 hours then unclamped to allow drainage. In addition to routine respiratory physiotherapy, patients were asked to move and change their position from the supine to left and right lateral decubitus positions to enhance distribution and drainage. This procedure was repeated every day for up to 3 successive days as required according to improvement of the opacity.

Patients in both groups were evaluated by:

1- Daily plain chest radiographs (CXR). In our study, classification of CXR results followed method used in the study done by Brockelsby and associates [2], where size of pleural effusion or collection estimated by the recognized method of counting intercostal spaces (ICS) from costophrenic angle (1 ICS =small- localized collection, 2–3 ICS= medium collection, large collection if ≥4 ICS).

2- Amount and character of daily chest tube drainage

3- Chest computed tomography (CT) was done after the course of chemical fibrinolysis was completed. Our classification of CT results based on the study done by Moy et al. [8] who developed and validated a simple rule for quantitating pleural effusion size on CT scan with a three-point scale based on the anteroposterior (AP) dimension, collection classified to small, moderate, and large sizes based on the AP quartile and maximum AP depth.

STATISTICAL ANALYSIS

Data were collected, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance:

- Chi Square Test ($\chi 2$): was used to study comparison and association between two qualitative variables. Fisher's Exact: correction for

chi-square when more than 20% of the cells have expected count less than 5. t-Test: was used for comparison between two groups having quantitative variables with normal distribution (for parametric data).A P-value of < 0.05 was considered statistically significant &<0.001 for high significant result for two tailed tests.

RESULTS

Patient demographics: the average age of our patients was 38±11years in first group and 40±7 years in second group. Male patients represented 70% (14 patients) in group I and 65% (13 patients) in group II without significant difference between both groups. All patients were sustained blunt thoracic trauma except 1 patient in group II who had penetrating injury. Fracture rib(s) observed in most of our patients in both groups (14 patients in group I and 16 patients in group II) ([able 1]. The average time between trauma and starting fibrinolytic protocol was 4±2.4 days. **In Alteplase group I** marked improvement and nearly complete resolution of clotted hemothorax occurred in 11 patients after the first dose of Alteplase therapy documented by chest X ray and CT examination. The other 9 patients were similarly improved after the second dose. So, no patient in this group was in need for the full course of Alteplase (3 doses). Moreover, Intrapleural instillation of Alteplase noted to be followed initially by significant drainage of serosanguineous fluid that was cleared and decreased rapidly, with dramatic improvement of chest tube drain. No patient in this group suffered from any bleeding complication (e.g. bleeding from nose, hematuria, blood tinged sputum …etc.) [Fig. 1] **In Streptokinase group II** complete improvement of CXR and CT after first dose of streptokinase therapy occurred in 6 patients with almost complete absorption of clotted blood. After the second dose 3patients were improved and 5 other patients were improved after the third dose. Minimal to small collections were found in 3 patients after full course not clearly justifying for surgical intervention, so we conserve them with close outpatient clinic follow up for 1 month, by the end of follow up period collections were almost disappeared. Full courses of intrapleural streptokinase failed to clear and improve 3 patients with persistent residual large pleural collection that necessitating surgical treatment in form of VATS drainage in 2 patients and thoracotomy for drainage and decortication in one patient [Fig. 1].

Bleeding complications: were not encountered in any patient in Alteplase group. It was only noted in streptokinase group where 1 patient complained of clinically insignificant blood tinged sputum and 1 patient complained of bleeding per nose, both of them controlled spontaneously with conservative treatment and did not need any specific therapy.

Table1: preoperative characteristics of patients in both group

Characteristic	Group 1	Group 2	P value
Age (years)	38± 11	40±7	NS
Gender			
-male	14 (70%)	13 (65%)	NS
-female	6 (30%)	7 (35%)	NS
Type of injury			
Blunt	20 (100)	19 (95%)	NS
penetrating	0 (0%)	1 (5%)	NS
Fracture rib(s)	14 (70%)	16 (80%)	NS

Group 1 =Alteplase group, Group 2 streptokinase group, data expressed as numbers /percentage. P value is significant if less than 0.05. NS =non-significant.

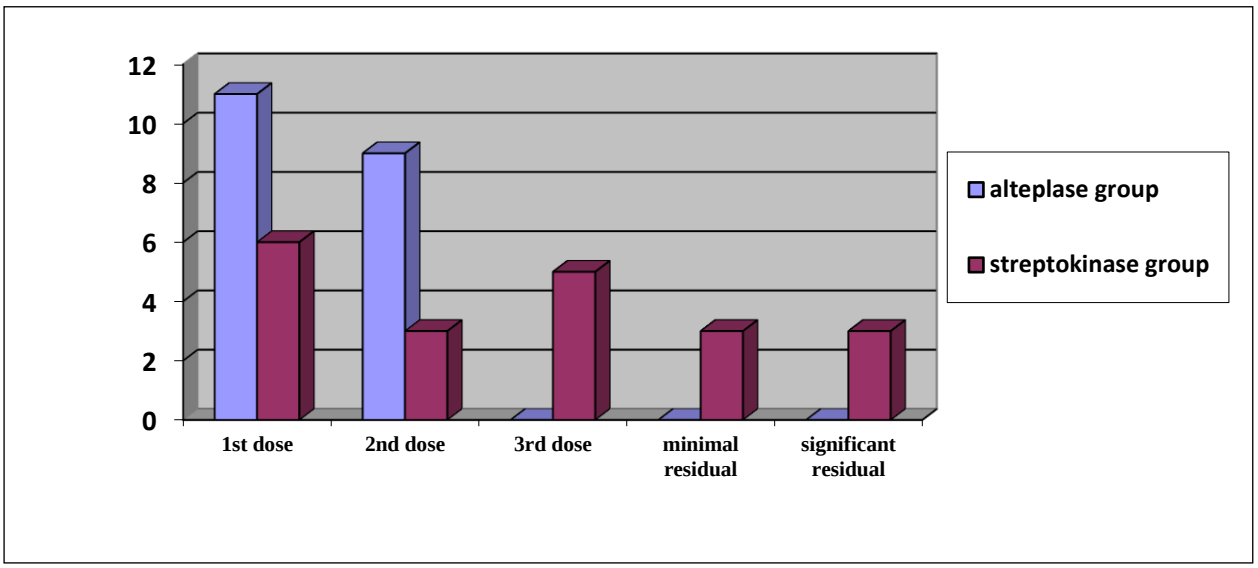

Figure 1: outcomes of patients in both groups after administration of fibrinolyic protocols (after 1st,2nd,3rd doses, patients who showed minimal or significant residual clotted hemothorax after 3rd dose).

DISCUSSION

Successful use of fibrinolyic agents in management of loculated empyema or hemothorax or was first described the in 1949 by **Sherry and associates** in a series of 23 patients [10] retained clotted traumatic hemothorax still represents a challenge for thoracic and trauma surgeons due to its known complications that include empyema, pneumonia, fibrothorax and trapped lung in addition to its economic costs and burden to healthcare systems due to prolonged hospital stay of the patients [11]. Afterwards, numerous reports described the use and effectiveness of intra-pleural fibrinolytic in treatment of clotted hemothorax. However most of the literature discusses streptokinase and urokinase therapy despite the more current interest in intra-pleural t-PA. So, the present study compares the efficacy of tissue plasminogen activator (TPA) versus Streptokinase (SK) in treatment of traumatic clotted hemothorax. In developing countries like Egypt fibrinolyic therapy have special economic privilege for healthcare system when compared to surgical management wither VATS (which is not always available in many centers) or thoracotomy with its known expenses and risks. The results of our study revealed globally that both modalities of intra-pleural chemical fibrinolysis were safe, successful and useful in the treatment of clotted hemothorax. However, comparative results showed higher success rate of TPA protocol in comparison to SK protocol (in 100% of TPA group and 85% in SK group). **Inci and his colleagues** observed in their retrospective study similar results to our study. Intrapleural thrombolytic administration in 24 cases of retained hemothorax had overall 91.7% success where some patients showed complete resolution and others showed good but less than complete resolution of clotted hemothorax [11]. In a small number study, **Stiles et al (2014)** also observed similar success rate about 86% for Intrapleural TPA in hemothorax patients [7]. Ben-Or and co-workers also reported encouraging results with Intra-pleural Alteplase which was successful in 61.5% (8 of 13 patients) of their subgroup of patients presented with hemothorax [5]. **Barthwal and colleagues** compared 2 agents used for Intrapleural fibrinolysis SK versus UK. They had favorable results when they used both of them SK/UK with success rate 91.6% in traumatic hemothorax group of patients. They also reported equivalent response to either agent [4]. **Hendriksen and associates** reported slightly different results in their meta-analysis study including 225 patients with clotted hemothorax (1 RCT and 9 non-RCT) when compared TPA to other fibrinolytics. Both, TPA and other lytics had comparable results. TPA was successful in 83% of patients, while other lytic drugs had 86% success rate [6]. In a further step, **Makey** and his group reported a promising results in their experimental study when combine Intrapleural TPA with vibration technique (by attaching certain motor to the chest tube end outside the chest) in a pig model with hemothorax. This technique showed better drainage and clearance when compared to other agitation method they used [1]. One of the most important concerns for thoracic surgeons about use of intrapleural fibrinolyic in setting of post-traumatic clotted hemothorax is the theoretical possibility of increased bleeding complications. In the present study we found that our both protocols had excellent safety from that point. The protocol of Alteplase showed no bleeding complication at

all, while 1 patient in SK group had very minor and clinically insignificant bleeding from nose and other one had minimal blood tinged sputum, both of them stopped spontaneously on conservative treatment. Thus we can assume that both protocols were safe in our practice. This result matched with the study done by **Skeete and his colleagues** who conducted study on 41 patients, reported that one patient (2.4%) developed hematuria after TPA administration [12]. Also in similar study done by **Thommi and associates** who studied 120 patients, they found 2% rate of bleeding at the chest tube site and one patient required a blood transfusion [13]. In fact, other than thoracotomy, VATS is believed to be the best available modality for the management of clotted hemothorax with efficacy rates between 80% and 100% [14-15]. Also, a decision to proceed with an open thoracotomy can be made expeditiously at the time of VATS. However, VATS is not routinely available in many centers [16]. **The Eastern Association** for the Surgery of Trauma performed meta-analysis to clarify the best option for treatment of retained traumatic hemothorax, they found that in centers with VATS facility, it may have had better results than thrombolytic therapy when performed early VATS within 4 days or less [17]. On contrary, **Kumar and his associates** documented in their controlled randomized study nearly equal resolve of retained hemothorax when fibrinolytic therapy used (SK 71%), or when VATS drainage used (72%) ($P > 0.99$). This results support the efficacy of fibrinolytic therapy that deserves more attention before proceeding with VATS with its known limitations [18]. Other researches recommended intrapleural fibrinolytic therapy as a first-line therapy in traumatic hemothorax before proceeding to mini-thoracotomy or pleural decortications [11]. In summary, fibrinolyic therapy had favorable results that deserve to be tried as primary solution in clotted traumatic hemothorax before shifting to other surgical options specially in developing

CONCLUSIONS

Intra-pleural fibrinolytic therapy with both Alteplase and Streptokinase were safe and successful in our patients with traumatic clotted hemothorax. Alteplase had better outcome with dramatic improvement in collection; chest tube drain and pleural thickness without failure or need for further surgical intervention, and also no bleeding complications were observed in this group. Intra-pleural Alteplase therapy is a simple and valid option that may be tried before exposing such patients to known risks of surgical procedures and general anesthesia. Further larger number studies will help more to identify the best protocol for management of traumatic retained hemothorax.

Disclosure of potential conflicts of interest : no conflicts of interest.

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