



## Original Article

# Timing of Intrapleural Streptokinase administration for Managing Post traumatic Clotted Hemothorax

Ahmed M Abdelazim, Mahmoud M Abdel Azeem Mubarak

Department of Cardiothoracic Surgery, Faculty of Medicine, Banha University, Banha, Egypt

### Abstract

**Background:** The optimal timing of intrapleural fibrinolytic therapy with streptokinase for managing posttraumatic clotted hemothorax is controversial. This study investigated the appropriate timing for fibrinolytic therapy initiation using streptokinase in post-traumatic clotted hemothorax.

**Methods:** We conducted a randomized clinical study that included 60 patients with a clotted hemothorax recruited between December 2023 to July 2024. Patients were grouped according to the timing of intrapleural streptokinase injection into two groups. Group I (n= 30) included patients who received intrapleural streptokinase between day 3 and day 7, and Group II (n= 30) included patients who received streptokinase 7 days after the diagnosis of clotted hemothorax.

**Results:** There were no significant differences in age, sex, the prevalence of diabetes mellitus, hypertension, addiction, or smoking between the groups. The most common mode of trauma was stabbing wounds, with no difference in trauma mode or laterality between the groups. The number of streptokinase doses was significantly lower in patients who had streptokinase early ( $p<0.001$ ), and their total drainage after administration was significantly greater than that in those who had streptokinase late (275 (200–400) vs. 100 (100–150) ml,  $p<0.001$ ). The infection rate was higher in patients with late streptokinase administration (1 (3.33%) vs. 8 (26.67%),  $p= 0.026$ ). No bleeding was reported in either group. The length of hospital stay was significantly longer in patients with late streptokinase administration (8 (7--9) vs. 19 (17--20),  $p<0.001$ ). The success rate was 90% in the early group and 53% in the late group ( $p= 0.004$ ). One patient in the early group and 23 (77%) in the late group required further surgical evacuation ( $p<0.001$ ).

**Conclusion:** Early intrapleural administration of streptokinase (within 3–7 days of clotted hemothorax) appears to be more effective than late administration (after 7 days) for managing posttraumatic clotted hemothorax.

### KEYWORDS

Clotted hemothorax;  
Chest trauma;  
Fibrinolytic therapy;  
Streptokinase

### Introduction

Clotted hemothorax is an organized accumulation of retained blood in the pleural space that usually occurs after thoracic trauma [1].

Clotted hemothorax might increase the risk of infection and prolong hospital stay [2,3]. Managing clotted hemothorax is challenging, and wide-bore chest drains are usually insufficient.



Traditional treatment modalities for clotted hemothorax, such as surgical decortication or video-assisted thoracoscopic surgery, can significantly increase hospital stays, treatment costs, and the risk of complications, especially in critically ill patients [4]. Intrapleural fibrinolysis with streptokinase is an attractive alternative noninvasive strategy that can rapidly lyse organized clots and improve drainage without surgical intervention [5]. Streptokinase acts by activating plasminogen and converting it to the proteolytic enzyme plasmin, which degrades fibrin clots [6].

The optimal timing of intrapleural fibrinolytic therapy for managing posttraumatic hemothorax is a controversial issue. Early administration of fibrinolytic agents, especially in the first 24 hours, can promptly lyse fibrin deposits, improving chest drainage; however, it could be associated with an increased risk of bleeding [7,8]. On the other hand, delayed intrapleural fibrinolytic therapy could be associated with a lower risk of bleeding, but its efficacy is questionable [9]. As time passes, enzymatic degradation of the clot is thought to be

delayed; hence, some residual pleural loculations persist and may require further intervention to achieve complete resolution [10]. Recent studies have shown that delaying intrapleural streptokinase injection following chest tube insertion or failure of clot evacuation can prevent fibrinolytic hemorrhagic events [9], but clear guidelines are still lacking. Therefore, this study aimed to further investigate the appropriate timing for fibrinolytic therapy initiation using streptokinase in post-traumatic clotted hemothorax.

### Patients and Methods Design and setting

We conducted a randomized clinical trial that included 60 patients with clotted post traumatic hemothorax. Patients were recruited between December 2023 to July 2024 at a single tertiary referral center. The study received approval from the Institutional Review Board (IRB) of the Faculty of Medicine at Banha University, and informed consent was obtained from all participants.

Table 1: Comparison of the baseline characteristics between patients who received early streptokinase (Group I) and those who received late streptokinase (Group II) for managing posttraumatic clotted hemothorax

	Group I (n= 30)	Group II (n= 30)	p value
Age (years) (mean± SD)	38.67± 14.73	40.73± 12.07	0.555
Male n (%)	22 (73.33%)	19 (63.33%)	0.405
<b>Comorbidities n (%)</b>			
Diabetes mellitus	8 (26.67%)	4 (13.33%)	0.197
Hypertension	8 (26.67%)	5 (16.67%)	0.347
<b>Social history n (%)</b>			
Addict	9 (30%)	5 (16.67%)	0.222
Smokers	19 (63.33%)	15 (50%)	0.297
<b>Mode of trauma n (%)</b>			
Falling from height	6 (20%)	9 (30%)	0.808
Road traffic accident	9 (30%)	9 (30%)	
Shotgun	2 (6.67%)	1 (3.33%)	
Stab	13 (43.33%)	11 (36.67%)	
<b>Side n (%)</b>			
Right	14 (46.67%)	15 (50%)	0.796
Left	16 (53.33%)	15 (50%)	
<b>Time from trauma to admission (days) median (Q1- Q3)</b>	1 (1- 2)	1 (1- 1)	0.074

### Randomization and Blinding

The patients were randomly assigned into two equal groups according to the timing of intrapleural streptokinase injection. Group I (n= 30) included patients who received intrapleural streptokinase between day 3 and day 7, and Group II (n= 30) included patients who received streptokinase 7 days after the diagnosis of clotted hemothorax.

Randomization was achieved using a computer-generated random sequence, and allocation was concealed using sealed opaque envelopes. Blinding was maintained by ensuring that the postoperative care team was unaware of the group assignments.

### Patients

The study included adults (aged >18 years) who presented to our center with chest trauma of less than 10 days in duration. Patients were diagnosed with hemothorax, which failed adequate large-bore chest tube drainage for 3 days. Retained hemothorax was diagnosed in all patients via chest computed tomography (CT) scans. Patients who were allergic to streptokinase, had end-stage liver or renal disease, had coagulopathy, or had associated severe abdominal or head trauma were excluded from the study.

### Procedure

Patients were assigned to each group via blocked randomization. Blinding of the treating physicians and patients was not possible; however, data collection and analysis were performed without prior knowledge of group assignment. Streptokinase was administered intrapleurally at a dose of 250000 IU diluted in 50 ml of normal saline via the intercostal chest drain. The procedure was performed aseptically, and the tube was clamped for 2 hours after injection. The patients were instructed to change their position every 15 minutes, after which the clamp was removed. The chest drain was connected to an underwater seal with negative suction. The amount of drainage was calculated, and the streptokinase injection was repeated after 2 days. Assessment of the patients involved a thorough medical history and a series of investigations such as Laboratory tests included a complete blood

count (CBC), liver function tests (LFT), renal function tests (RFT), and the international normalized ratio (INR), Chest X-ray, Ct chest. In the case of residual hemothorax, a third dose was given and the close follow up done by Chest X-ray, CT chest till the patients discharged from hospital. After discharge to home, follow up done every 2 weeks in the 1st month and monthly in the 1st 3 months by Chest X ray.

### Data and outcomes

Baseline data included sex, age, comorbidities (diabetes, hypertension), social history (drug addiction and smoking), mode of trauma (blunt and sharp), and time from trauma to admission. The number of doses and total drainage from the chest tube after the administration of streptokinase were reported. The primary outcomes were the resolution of hemothorax and the need for surgical intervention. The secondary outcomes were the duration of hospital stay, infection (empyema or wound infection), and bleeding. We defined complete resolution as the complete evacuation of the retained hemothorax as diagnosed by chest CT. A partial response was diagnosed when there was minimal residual collection of less than 25% of the chest.

### Statistical analysis

Continuous data were evaluated for normality of distribution, and normally distributed data are presented as the means and standard deviations, whereas nonnormally distributed data are described as medians and interquartile numbers. Student's t test was used to compare normally distributed continuous variables, and the Wilcoxon test was used otherwise. Categorical data are presented as numbers and percentages and were compared via the chi-square test or Fisher's exact test whenever suitable. Ordinal logistic regression was used to assess factors associated with failure (classified as no failure, partial failure or complete failure), and logistic regression was used to evaluate the association with surgery. Odds ratios and their 95% confidence intervals are reported. Stata 18 (Stata Corp., College Station, TX, USA) was used for analysis. A p value of less than 0.05 was considered statistically significant.

Table 2: Comparison of outcomes between patients who received early streptokinase (Group I) and those who received late streptokinase (Group II) for managing posttraumatic clotted hemothorax

	Group I (n= 30)	Group II (n= 30)	p value
<b>Doses, n (%)</b>			
Two	26 (86.67%)	12 (40%)	<0.001
Three	4 (13.33%)	18 (60%)	
<b>Total drainage post injection (ml) median (Q1- Q3)</b>	275 (200- 400)	100 (100- 150)	<0.001
<b>Post administration CT, n (%)</b>			
Resolved	27 (90%)	2 (6.67%)	<0.001
Partial resolution	2 (6.67%)	5 (16.67%)	
No resolution	1 (3.33%)	23 (76.67%)	
<b>Infection n (%)</b>	1 (3.33%)	8 (26.67%)	0.026
<b>Failure n (%)</b>			
No	27 (90%)	16 (53.33%)	0.004
Partial	2 (6.67%)	5 (16.67%)	
Complete	1 (3.33%)	9 (30%)	
<b>Hospital stay (days) median (Q1- Q3)</b>	8 (7- 9)	19 (17- 20)	<0.001
<b>Surgery, n (%)</b>	1 (3.33%)	23 (76.67%)	<0.001

## Results

### Baseline characteristics

There were no significant differences in age, sex, the incidence of diabetes mellitus, hypertension, addiction, or smoking between the groups. The most common mode of trauma was stabbing wounds, with no difference in trauma mode or laterality between the groups. All patients were managed with a wide-bore chest drain size of 34 Fr (Table 1).

late ( $p < 0.001$ ). The infection rate was higher in patients with late streptokinase administration ( $p = 0.026$ ). No bleeding was reported in either group. The length of hospital stay was significantly longer in patients with late streptokinase administration ( $p < 0.001$ ). The success rate was 90% in the early group and 53% in the late group ( $p = 0.004$ ). One patient in the early group and 23 (77%) in the late group required further surgical evacuation ( $p < 0.001$ ) (Table 2).

Table 3: Factors associated with treatment failure

Failure	$\beta$ (95% CI)	p value
Late streptokinase	2.911 (0.955- 4.867)	0.004
Age	-0.008 (-0.08- 0.07)	0.839
Sex	1.121 (-1.24- 3.48)	0.351
Diabetes mellitus	2.096 (-0.1.9- 4.38)	0.073
Hypertension	0.035 (-1.98- 2.05)	0.973
Addiction	0.707 (-1.26- 2.67)	0.48
Smoker	0.263 (-2.61- 3.14)	0.857
Trauma mode	-0.217 (-1.23- 0.792)	0.674
Time of admission	-1.217 (-3.17- 0.74)	0.221

### Treatment and outcomes

The number of streptokinase doses was significantly lower in patients who had streptokinase early ( $p < 0.001$ ), and their total drainage after administration was significantly greater than that in those who had streptokinase

### Factors associated with the outcomes

Late streptokinase injection was the only factor associated with treatment failure ( $\beta$ : 2.911 (95% CI: 0.955–4.867),  $p = 0.004$ ) (Table 3). Similarly, late streptokinase was significantly associated with the need for surgery (Table 4).

Table 4: Factors associated with surgical intervention

Surgery	OR (95% CI)	p value
Late streptokinase	402.02 (14.52- 1112)	<0.001
Age	1.089 (1.001- 1.18)	0.05
Sex	1.24 (0.08- 19.70)	0.88
smoker	0.32 (0.01- 9.24)	0.504
Trauma mode	2.81 (0.78- 10.18)	0.116
Time of admission	1.36 (0.13- 14.07)	0.795

## Discussion

An intrapleural streptokinase is a therapeutic option for managing posttraumatic clotted

hemothorax. This therapeutic technique works by dissolving fibrin clots and facilitating the drainage of residual blood and loculated effusions, particularly when traditional methods such as tube thoracostomy are insufficient [11,12]. The optimal time between stratified clotted hemothorax and streptokinase injection has not been established. This study compared early (3–7 days) vs. late (>7 days) intrapleural injection of streptokinase for managing clotted hemothorax. Patients who received early streptokinase therapy achieved a higher success rate and needed less surgical intervention to evacuate residual hemothorax. Early streptokinase injection could have the potential advantage of facilitating lysis of the clotted hemothorax, as the risk of loculations and fibrosis increases with time. This could be reflected in the increased success of the technique [13]. Furthermore, we reported no bleeding episodes with either early or late streptokinase administration; however, the infection rate was higher with late administration. The reported hospital stay was longer in patients with delayed administration, which could be attributed to the increased time from the onset of clotted hemothorax to the administration of streptokinase and the frequent need for surgical intervention in the delayed group, which increased the duration of stay.

Our results are consistent with those of Elgazzar and colleagues' study, which reported a higher success rate following early intrapleural streptokinase injection for posttraumatic clotted hemothorax. They reported a 60% complete resolution rate compared with 90% in our series in patients with early streptokinase administration [9]. No hemorrhagic complications were reported, similar to our series. The high success rate in our series could be attributed to the high rate of sharp chest injuries. Huang and colleagues reported a complete response of 76% after urokinase administration in patients with residual hemothorax after lung surgery [13]. However, they reported one case of bronchopleural fistula. In a multicenter retrospective study, 86% of patients with retained or clotted hemothorax treated with intrapleural streptokinase achieved successful resolution of their clotted hemothorax, with a notable increase in chest tube output

following treatment [14]. Another study revealed that intrapleural streptokinase effectively reduced pleural thickening and adhesion formation in experimental models, supporting its use in clinical settings without intercostal tubes [15]. Kimbrell and colleagues reported a success rate of 92% within 3 days after the use of streptokinase or urokinase for retained post traumatic hemothorax [16].

The technique has proven safe in several studies. Weinstein and colleagues reported that no bleeding episodes, either local or systematic, were associated with intrapleural administration of tissue plasminogen activators [17]. A similar finding was reported in Feola and associates' study on the use of tissue plasminogen activators in children with parapneumonic effusion [18]. This is similar to our study, in which no bleeding was reported. However, cases of minor bleeding [19] and rarely major systematic bleeding have been reported [20].

### Implications

This study suggests that early administration of intrapleural streptokinase is more effective than late administration for managing posttraumatic clotted hemothorax. Early streptokinase administration could reduce the need for surgical intervention. Therefore, early intrapleural injection of streptokinase is recommended for the appropriate management of clotted hemothorax to mitigate the risk of surgical intervention and increase treatment success.

### Study Limitation:

This study has several limitations, including its single-center experience, and the generalizability of the results to other centers may not be applicable. Although there were significant differences in the outcomes between the groups, the sample size was small and did not provide wide variation in the baseline data, confirming that the techniques could be effective for all types of chest trauma. Furthermore, a larger sample size may be needed to provide full insight into the potential adverse effects of intrapleural streptokinase administration.

## Conclusion

Early intrapleural administration of streptokinase (within 3–7 days of clotted hemothorax) appears to be more effective than late administration (after 7 days) for managing posttraumatic clotted hemothorax. Early streptokinase injection may facilitate easier lysis of the clotted hemothorax and reduce the need for surgical intervention. Further research with larger sample sizes is needed to confirm the optimal timeframe and establish the safety profile of this therapeutic approach.

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