ORIGINAL ARTICLE

Efficacy and safety of high dose versus low dose streptokinase for treatment of submassive pulmonary embolism

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Abstract Pulmonary embolism (PE) remains a major cause of morbidity and mortality in the general population, the established treatment for PE is anticoagulation. It has previously been demonstrated that thrombolytic therapy can be lifesaving in patients with massive PE (haemodynamic instability and right heart failure). However, the use of thrombolytic therapy in patients with submassive PE (haemodynamically stable) remains a controversial topic. Recent clinical studies, however, support evidence that thrombolysis may favorably affect the outcomes in a wider spectrum of high risk PE patients presenting with right ventricular dysfunction (RVD) as evidenced by decreased right ventricular end diastolic diameter (RVEDD), disappearance of paradoxical septal motion (PSM), and tricuspid regurge (TR) as well as decrease in the pulmonary artery pressure. The aim of this study was to evaluate the efficacy and safety of high dose streptokinase (SK) in 1 h versus low dose SK in 24 h in patients with submassive PE and RVD (high risk PE). The study included 60 patients (28 males and 32 females, mean age 45.5 ± 13.6 years) with submassive PE (positive spiral CT chest) and RVD (proved by echocardiography). Those without contraindications to SK were randomly assigned to receive either high dose (group I) or low dose (group II) of SK. Those with contraindication(s) to SK received anticoagulation (group III). Echocardiography was done before and 72 h after treatment. Right ventricular dysfunction (RVEDD, PSM, and TR) and mean pulmonary artery pressure (PAP) improved significantly 72 h after treatment in

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groups I and II, while a slight improvement in PAP was observed after treatment in group III. No significant difference was noticed between groups I and II regarding the effect of treatment on RVD or PAP. Statistically nonsignificant difference was found between groups I and II regarding the complications of SK, however a slightly higher risk of bleeding was observed in group I (high dose SK). No significant difference was found between the three groups regarding the mortality. These data suggest that SK can rapidly and safely reverse the pulmonary hypertension and RVD in contrast to anticoagulation. Both protocols of SK are equieffective in rapid reversal of RVD and pulmonary hypertension. Both protocols were safe as proved by absence of difference in mortality over anticoagulant group.

1. Introduction

Pulmonary embolism (PE) is a common disorder associated with substantial morbidity and mortality; autopsy series have shown that PE is responsible for 15% of all in-hospital deaths.[1]

Anticoagulants remain the standard of care for venous thromboembolism (VTE); anticoagulation prevents clot propagation and allows endogenous fibrinolytic activity to dissolve existing thrombi, a process that typically occurs over several weeks or months. Thrombolytic therapy, by actively dissolving thromboembolic, offers several potential advantages over anticoagulation in the treatment of patients with VTE.[2]

Thrombolysis is an established treatment for patients with massive PE and haemodynamic instability (cardiogenic shock or persistent arterial hypotension). In contrast, the effect of thrombolytic agents on the outcome of haemodynamically stable patients who have submassive PE has been debated for decades.[3,21,22]

Registry data indicate that right ventricular dysfunction (RVD) in patients with PE is associated with an increased risk of fatal outcomes even in patients who are haemodynamically stable.[4,18,19]

The indication and rationale for thrombolysis in submassive PE remain debatable as no large-scale randomized controlled clinical trials comparing thrombolytic agents, or thrombolysis and anticoagulation to anticoagulation alone have been performed.[5,18,19,21]

The aim of this study was to compare the efficacy and safety of high dose streptokinase (SK) in 1 h versus low dose SK in 24 h in patients with submassive PE and RVD.

2. Patients and methods

Sixty patients (28 males and 32 females) with submassive PE and RVD were enrolled in the study. The mean age was 45.5 ± 13.6 years (range 22–75 years).

2.1 Inclusion criteria

(a) Proven PE by spiral CT scan of the chest. (b) Evidence of pulmonary hypertension and/or RVD (RV dysfunction) including increased right ventricular end diastolic diameter (RVEDD), paradoxical inter-ventricular septal motion (PSM), and tricuspid regurge (TR). (c) Patients age range 18–75 years. (d) Patients referred within 14 days after the onset of symptoms.

2.2. Exclusion criteria

(a) Normal echocardiographic examination (minor PE). (b) Haemodynamic instability or cardiogenic shock (massive PE). (c) Previous PE.

2.3. Protocol

Patients without contraindications to thrombolysis were randomly assigned to receive either high dose SK; 1,500,000 U over 1 h (group I; included 15 patients) or low dose SK; 250,000 U over 30 min followed by 100,000 U/h for 24 h (group II; included 25 patients). Thrombolysis was followed by anticoagulant therapy (unfractionated heparin and warfarin). Those with contraindication(s) to thrombolysis received anticoagulant therapy (group III; included 20 patients).

2.4. Contraindications for thrombolysis (risk of bleeding)

Cerebrovascular accident, intracranial trauma or surgery within the last 2 months; active intracranial disease (neoplasm, aneurysm, vascular malformation); major internal bleeding within past 6 months; uncontrolled hypertension (systolic blood pressure > 200 mmHg, diastolic blood pressure > 110 mmHg); bleeding diathesis, coagulopathies or platelet count < 100,000 mm³; recent major surgery, organ biopsy or labour (within 10 days); recent trauma; infective endocarditis/pericarditis; pregnancy; aortic aneurysm; hemorrhagic retinopathy; decompensated liver disease, and renal failure.[7]

2.5. Pre-treatment evaluation

This included recording of the vital signs, arterial blood gases, ECG, chest X-ray (CXR), study of the venous system of the lower limbs using Duplex ultrasound, post-contrast spiral CT of the chest, echocardiography (for measurement of PAP and evidence of RVD: RVEDD, PSM, and TR), and laboratory tests (CBC, INR, PTT, and creatinine).

2.6. Post-treatment evaluation

Seventy-two hours after treatment the following data were reevaluated: vital signs, arterial blood gases, and echocardiography (for re-measurement of PAP and detection of RVD: RVEDD, PSM, and TR).

2.7. Statistics

Data were analyzed using SPSS program version 10. Qualitative data were presented as a percent and comparison between groups was done by χ^2-test. Quantitative data were tested for normality by Kolmogrov–Smirnov test. Normally distributed data were presented as mean $\pm$ SD. Paired t-test was used for comparison within groups and unpaired t-test was used to compare between two groups. One Way ANOVA was used to compare between more than two groups. A P-value < 0.05 was regarded as significant.

3. Results

3.1. Respiratory rate and heart rate changes

There was significant decrease in the heart rate and respiratory rate after treatment in the three groups. No significant difference regarding the post-treatment changes of heart rate and respiratory rate among the three groups was found (Table 1).

3.2. Arterial blood gases changes

The PaO_2 and $PaCO_2$ increased significantly after treatment in the three groups. The alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$] decreased significantly in the three groups. There was no significant difference regarding post-treatment changes in PaO_2, $PaCO_2$, and $P(A\text{-}a)O_2$ among the three groups (Table 2).

3.3. Echocardiographic changes

Right ventricular dysfunction (RVEDD, PSM, and TR) and mean pulmonary artery pressure (PAP) improved significantly 72 h after treatment in groups I and II, while a statistically nonsignificant improvement in PAP was observed after treatment in group III, with no any improvement in the RVD (RVEDD, PSM, and TR) in that group (Tables 3–5).

There was a significant difference regarding post-treatment changes in RVEDD and PAP among the three groups (Table 6); highly significant difference was found between groups I + II versus group III (Table 7) while no significant difference could be seen between groups I and II (Table 8).

The post-treatment changes in PSM and TR were not significantly different between groups I and II (Table 9).

3.4. Complications of SK therapy

Complications following treatment with SK in 40 patients (groups I and II) were as follow: transient low grade fever in four patients (10%), transient hypotension in three patients (7.5%), major bleeding (GIT) in one patient (2.5%), and

Table 1 Changes of heart rate (HR) and respiratory rate (RR) (as a percentage of the pre-treatment values) in groups I, II, and III.

	Group I	Group II	Group III	P value
HR	-18.2 ± 8.4	-24.9 ± 6.1	-21.8 ± 8.7	0.136
RR	-22.0 ± 7.7	-24.8 ± 6.4	-22.7 ± 4.6	0.431

Table 2 Changes of arterial blood gases parameters (as a percentage of pre-treatment values) in groups I, II, and III.

	Group I	Group II	Group III	P value
PaO_2	19 ± 9.5	25 ± 14.8	20 ± 20.4	0.606
$PaCO_2$	7.7 ± 6.2	9 ± 13.3	13.3 ± 15.6	0.494
$P(A\text{-}a)O_2$	-33.7 ± 8.7	-37.2 ± 9.3	-35.6 ± 15.5	0.802

Table 3 Changes in RVEDD, PAP, PSM, and TR after treatment in group I.

	Pre-treatment	Post-treatment	P value
RVEDD (cm)	3.4 ± 0.3	2.7 ± 0.2	0.000
PAP (mmHg)	50.9 ± 7.7	39.0 ± 6.6	0.000
PSM			
Present (%)	63.6	0	0.005
Absent (%)	36.4	100	
TR grade			
0 (%)	0	25	0.005
1 (%)	18.2	62.5	
2 (%)	54.5	12.5	
3 (%)	27.3	0	

Table 4 Changes in RVEDD, PAP, PSM, and TR after treatment in group II.

	Pre-treatment	Post-treatment	P value
RVEDD (cm)	3.1 ± 0.3	2.5 ± 0.2	0.000
PAP (mmHg)	53.1 ± 4.8	42.6 ± 5.8	0.000
PSM			
Present (%)	47.4	0	0.000
Absent (%)	52.6	100	
TR grade			
0 (%)	21.1	41.2	0.000
1 (%)	15.8	58.8	
2 (%)	63.2	0	
3	0	0	

Table 5 Changes in RVEDD, PAP, PSM, and TR after treatment in group III.

	Pre-treatment	Post-treatment	P value
RVEDD (cm)	3.0 ± 0.4	3.0 ± 0.4	1.0
PAP (mmHg)	47.0 ± 9.4	44.4 ± 6.8	0.05
PSM			
Present (%)	50	50	0.317
Absent (%)	50	50	
TR grade			
0 (%)	60	57.9	1.0
1 (%)	25	26.3	
2 (%)	15	15.8	
3	0	0	

allergy in one patient (2.5%) (Table 10). No significant difference was found between groups I and II regarding the complications of SK (Table 11).

Table 6 Changes of right ventricular end diastolic diameter (RVEDD) and mean pulmonary artery pressure (PAP) (as a percentage of pre-treatment values) in groups I, II, and III.

	Group I	Group II	Group III	P value
RVEDD	−19.5 ± 4.2	−20.5 ± 6.8	0.000	0.000
PAP	−23.4 ± 4.8	−19.9 ± 5.7	−4.9 ± 6.4	0.000

Table 7 Changes of right ventricular diameter (RVEDD) and mean pulmonary artery pressure (PAP) (as a percentage of pre-treatment value) in groups (I + II) versus group III.

	Group I + II	Group III	P value
RVEDD	−20.1 ± 6	0.00	0.000
PAP	−21.1 ± 5.6	−4.9 ± 6.4	0.000

Table 8 Changes of right ventricular diameter (RVEED) and mean pulmonary artery pressure (PAP) (as a percentage of pre-treatment value) in groups I and II.

	Group I	Group II	P value
RVEDD	−19.5 ± 4.2	−20.5 ± 6.8	1.0
PAP	−23.4 ± 4.8	−19.9 ± 5.7	0.536

Table 9 Changes in paradoxical septal wall motion (PSM) and tricuspid regurge (TR) after treatment in groups I and II.

	Group I (%)	Group II (%)	P value
PSM			
Present	0	0	1.0
Absent	100	100	
TR grade			
0	25	41.2	0.3
1	62.5	58.8	
2	12.5	0	
3	0	0	

Table 10 Complications of SK therapy in groups I and II (30 cases).

	No	%
Fever	4	10
Hypotension	3	7.5
Major bleeding (GIT)	1	2.5
Allergy	1	2.5

Table 11 Comparison of complications of SK therapy between groups I and II.

	Group I (%)	Group II (%)	P value
Fever	18.2	10.5	0.6
Hypotension	9.1	10.5	0.9
Major bleeding (GIT)	9.1	0	0.2
Allergy	0	5.3	0.4

3.5. Mortality

There was no mortality in group I, one death in group II (4%), and one death in group III (5%). No significant difference was found between the three groups regarding the mortality.

4. Discussion

This study was planned to evaluate the efficacy and safety of thrombolytic (streptokinase) therapy in patients with submassive PE and right ventricular dysfunction. The recovery of right ventricular function was considered as a marker of thrombolysis efficacy.[8,20]

The study included 60 patients with high risk submassive PE (with RVD) as proved by spiral CT and RVD on echocardiogram. Three therapeutic protocols were used, those with RVD and without a contraindication for thrombolysis were randomized to receive either a high dose, short term streptokinase (SK) (1,500,000 IU over 1 h) or low dose, long term streptokinase (250,000 IU over 30 min then 100,000 IU every hour for 24 h). Those with RVD and with a contraindication for thrombolytic treatment received anticoagulant therapy alone.

4.1. High dose SK (group I)

The efficacy of treatment was proved by rapid recovery of the right ventricular function on echocardiogram. RVEDD decreased significantly from 3.4 ± 0.3 to 2.7 ± 0.2 cm, PAP decreased by 23.4%, PSM and TR severity improved in all patients. These data suggest a rapid reversal of pulmonary hypertension and right ventricular dysfunction after thrombolysis.

The efficacy of high dose SK in treatment of PE with RVD was confirmed in previous studies. Jerjes-Sanchez et al.[9] studied the effect of high-dose and short term SK protocol (1,500,000 IU over 1 h) in patients with massive PE. Patients randomly received either SK or heparin therapy. All patients who received heparin alone died, whereas no deaths occurred in the SK group. Also in another study Jerjes-Sanchez et al.[6] used high dose and short term SK in 40 patients with massive PE and RVD, 40% of patients were shocked. Survivors showed improved haemodynamic and echocardiogram parameters as early as 24 h post-treatment.

Meneveau et al.[10] studied the effect of high dose SK in 43 patients with massive PE showing a rapid reversal of pulmonary hypertension and RVD.

4.2. Low dose SK (group II)

As with the high dose SK protocol; the efficacy of treatment was proved by rapid recovery of the right ventricular function on echocardiogram. The RVEDD significantly decreased from 3.1 ± 0.3 to 2.5 ± 0.2 cm, PAP decreased by 19.9%, TR severity and PSM improved in all patients. Again, the results suggest that low dose long term SK is also effective in reversing the pulmonary hypertension and RVD.

The efficacy of low dose SK in PE was tested in previous studies; *The Urokinase-Streptokinase Embolism Trial*[11,20] studied the effect of low dose SK (250,000 U over 30 min then 100,000 IU/h for 24 h). There was improvement in angiographic severity scores and haemodynamic variables 24 h post-treatment. Ly et al.[12] studied the effect of (250,000 IU

SK bolus then 100,000 IU/h for 72 h) in 14 patients with massive PE. The degree of angiographic improvement was significantly greater in the SK group compared to the heparin group. Meneveau et al.[13] studied the effect of SK (250,000 U bolus then 100,000 IU every hour for 12 h) in 25 patients with massive PE. A rapid improvement in pulmonary artery pressure and pulmonary vascular resistance were observed.

4.3. High dose versus low dose SK

In the present study, the two protocols using SK (high dose and low dose) were equieffective and safe as proved by absence of significant difference between the degrees of improvement in the RVD however the low dose SK was associated with less risk of major bleeding (Table 11), this finding is similar to that found by Wang et al.[20], major (GIT) bleeding had occured in one patient in group I, which represent 2.5% of the total SK patients.

4.4. Thrombolysis versus anticoagulation (group III)

Twenty patients with submassive PE and RVD received heparin only due to presence of contraindication to SK. The response was measured 72 h post-treatment showing significant changes in HR, RR, and ABGs parameters. But a statistically nonsignificant decrease in PAP and no improvement in RVD (RVEDD, PSM, and TR) were observed. Although there were no significant difference between the SK and the heparin treatment regarding the post-treatment changes in HR, RR, blood and ABGs parameters, only patients who received SK showed a significant improvement in RVD. Also the decrease in PAP was significantly larger after the SK treatment compared to the heparin treatment. These data suggested that only SK can rapidly reverse the pulmonary hypertension and RVD.

These results support the findings of previous studies comparing heparin and streptokinase in PE. Ly et al.[12] compared heparin with SK treatments; the greater improvement was evaluated angiographically in SK group. Hamel et al.[14] compared 64 patients treated with thrombolysis with 64 patients treated with heparin only (submassive PE); the improvement in lung perfusion was 42% and 65% in the heparin and the SK groups, respectively. Goldhaber et al.[15] reported that in patients with submassive PE treated with heparin the RV function improved by 17% only.

4.5. Complications of thrombolysis

Apart from major bleeding (GIT) in one patient (2.5%) who received high dose SK, other complications were minor. Minor complication included low grade fever (10%), transient hypotension (7.5%) and allergy (2.5%). These results are comparable to the results reported by others; Jerjes-Sanchez et al.[6]; reported 1 case (2.5%) with major hemorrhage and 4 cases (10%) with minor complications such as transient hypotension, skin allergy and rigors. Meneveau et al.[10]; reported 3 cases (7%) with major hemorrhage in patients who received high dose SK.

In this study there was no mortality in group I (high dose SK) this was similar to the finding of Meneveau et al.[10] who reported no mortality with high dose, while Jerjes-Sanchez et al.[6] reported 12.5% mortality in patients receiving high dose SK. One death (4%) was observed in group II (low dose SK). Similar figures were reported in previous studies using a similar

protocol. Ly et al.[12] reported 7.1% mortality while Meneveau et al.[13] reported 4% mortality. The mortality rate in heparin group was (5%) similar to those previously reported by others using heparin treatment; Thabut et al.[16] reported 5.8% mortality and Goldhaber et al.[15] reported 3.6%. In the present study no significant difference in mortality was found between the three groups. This is in agreement with Agnelli et al.[17] and Thabut et al.[16] who concluded that thrombolytic therapy conferred no mortality disadvantage over heparin. This is in contrast to Jerjes-Sanchez et al.[9] where all patients who received heparin died while those who received SK survived and this was the only study which demonstrated survival advantage in thrombolytic therapy over heparin therapy.

In conclusion; in contrast to heparin; the SK treatment rapidly and safely reverse the RVD and pulmonary hypertension in patients with submassive PE. The low dose SK was as effective as the high dose SK treatments with less risk of bleeding. The SK treatment was as safe as heparin as regards complications and mortality.

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