Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment

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Acute venous thromboembolism includes deep vein thrombosis of the leg and pulmonary embolism. It is a frequently occurring disease with a potentially fatal outcome. The clinical course is characterised by short-term as well as long-term sequelae. The main goal for therapy therefore, is to prevent extension and recurrence of the disease in the acute phase and to prevent long-term complications such as the post-thrombotic syndrome and pulmonary hypertension. Although deep vein thrombosis and pulmonary embolism traditionally are defined as two different clinical entities, they are now more seen as manifestations of one and the same disease, venous thromboembolism. Venographic studies in patients with pulmonary embolism revealed that around 80% of them have evidence of thrombosis in the leg. Vice versa, in 50% to 80% of patients with deep vein thrombosis, silent pulmonary embolism is present as revealed by ventilation perfusion scintigraphy. However, most of the available treatment studies were designed and executed separately for the two diseases. Therefore, in this chapter firstly the epidemiology, natural history and prognosis of deep vein thrombosis will be briefly discussed followed by a review of the anticoagulant and fibrinolytic therapy for this disease. Subsequently, the same issues regarding pulmonary embolism will be discussed and finally some recommendations will be made.
Deep Vein Thrombosis

Background - epidemiology, natural history and prognosis

Deep vein thrombosis of the leg is a common disease with an annual incidence of 1-2 per 1000 individuals per year. The acute symptoms consist of redness, swelling and pain due to venous obstruction and inflammation. Later sequelae include recurrent deep vein thrombosis or pulmonary embolism and the post-thrombotic syndrome. Follow-up studies of patients with a first episode of thrombosis showed that the cumulative risk for recurrent disease is about 30% over 8 years and that approximately 50% of patients will develop the post-thrombotic syndrome in the subsequent two years following the thrombotic event. The main goal of therapy, therefore, is to prevent extension or recurrence of the disease and to impede the late effects of venous thrombosis. To achieve this goal different therapeutic approaches are available, such as thrombectomy, fibrinolytic therapy and treatment with anticoagulant drugs. The most accepted treatment for deep vein thrombosis is anticoagulant therapy.

Anticoagulant therapy – heparin and vitamin K antagonists

It is current practice to treat patients with proven acute deep vein thrombosis (DVT) initially with heparin or low molecular weight heparin (LMWH) for a period of 5 to 7 days, followed by vitamin K antagonists for at least 3 months. At least 14 well-designed studies have compared the treatment of aPTT adjusted heparin with fixed-dose LMWH in the initial phase of DVT treatment. During a 3 to 6 months follow-up period, 4.3% of the patients treated with LMWH experienced recurrent thrombotic events as compared to 5.6% in the patients who received unfractionated heparin (odds ratio 0.76, 95% confidence interval [CI]: 0.57-1.01). Major bleeding occurred in 1.3% of the patients in the LMWH group and in 2.1% of the patients treated with standard unfractionated heparin (odds ratio 0.60, 95% CI: 0.39-0.93). Hence, the current therapy of LMWH and vitamin K antagonists is very effective in preventing recurrent disease with a low risk of bleeding. It is, however, unknown what the efficacy is in preventing the post-thrombotic syndrome. The etiology of the post-thrombotic syndrome is thought to be caused by venous valve damage, regurgitation of the blood, venous hypertension and stenosis. Early clot lysis could be an attractive option to prevent valve damage, persistent stenosis and in the end venous hypertension. Therefore, fibrinolytic therapy may be useful.

Fibrinolytic therapy

Recently, Wells and Forster reviewed the available literature regarding fibrinolytics in the treatment of deep vein thrombosis. A total of 7 randomised trials have compared treatment of streptokinase with unfractionated heparin in the treatment of patients with proximal deep vein thrombosis. Streptokinase was administered as a bolus injection (range 50,000-600,000 U) followed by continuous infusion (100,000-200,000 U per hour) over a time period ranging from one to seven days. Outcome
Table 1. The efficacy (as assessed by repeat venography) and safety of streptokinase versus heparin for the initial treatment of acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment Groups</th>
<th>Significant lysis</th>
<th>Major bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T (H)</td>
<td>H</td>
<td>T (H)</td>
</tr>
<tr>
<td>Robertson 1968</td>
<td>16</td>
<td>Streptokinase + Heparin</td>
<td>5.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>20</td>
<td>Streptokinase + Heparin</td>
<td>7.10</td>
<td>2.10</td>
</tr>
<tr>
<td>Robertson 1970</td>
<td>16</td>
<td>Streptokinase + Heparin</td>
<td>5.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>34</td>
<td>Streptokinase + Heparin</td>
<td>10.19</td>
<td>1.15</td>
</tr>
<tr>
<td>Porter 1975</td>
<td>50</td>
<td>Streptokinase + Heparin</td>
<td>13.24</td>
<td>8.26</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>51</td>
<td>Streptokinase + Heparin</td>
<td>17.26</td>
<td>0.25</td>
</tr>
<tr>
<td>Arnesen 1978</td>
<td>42</td>
<td>Streptokinase</td>
<td>15.21</td>
<td>5.21</td>
</tr>
<tr>
<td>Total</td>
<td>229</td>
<td>Streptokinase + Heparin</td>
<td>72/117</td>
<td>18/112</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(62%)</td>
<td>(16%)</td>
<td>(15%)</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) | 3.9 (2.5-6.0) | 2.8 (1.2-6.2)
Test for heterogeneity | p=0.21 | p=0.85

T=Thrombolysis, H=Heparin

measures were short-term efficacy, adverse events and incidence of the post-thrombotic syndrome. Short-term efficacy was evaluated by comparing pre and post treatment venograms. A good response was defined differently in the various studies and included moderate to substantial clot lysis, > 50% lysis, or grade III to IV lysis. Adverse events were defined as major bleeding, or death. The presence of the post-thrombotic syndrome was assessed clinically with knowledge of treatment allocation and in all studies patients were lost to follow-up, hence these data are likely to be biased. Table 1 shows the short-term efficacy results and bleeding rates of the seven studies. It is clear from this table that the administration of streptokinase is associated with a 4-fold greater significant clot lysis at the cost of a 3-fold increase in bleeding. The rate of major haemorrhage was 15% in streptokinase treated patients as compared to 5% in heparin recipients. Three other studies have compared rtPA and unfractionated heparin with placebo and unfractionated heparin in patients with proximal DVT. In one study rtPA was given as a bolus (range 0.5 mg/kg over 4 hours - 0.5 mg/kg over 8 hours) and repeated after 24 hours, in another study rtPA was administered as a continuous infusion (0.05 mg/kg/hour over 1 day), while in the third study patients received a continuous infusion of 100 mg on day 1, followed by a continuous infusion of 50 mg on the second day. Outcome events were venographic clot lysis, major hemorrhage and pulmonary embolism. In Table 2, the results with respect to efficacy (>50% clot lysis) and safety of these three studies are summarised. Again there is a
Table 2. The efficacy (as assessed by repeat venography) and safety of rt-PA versus heparin for the initial treatment of acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Treatment groups</th>
<th>Significant lysis</th>
<th>Major bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T (-H)</td>
<td>rtPA-Heparin</td>
<td>H</td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>32</td>
<td>n.a.</td>
<td>rtPA</td>
<td>8/25</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>65</td>
<td>15/53</td>
<td>Heparin</td>
<td>0/12</td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>83</td>
<td>13/41</td>
<td>rtPA-Heparin</td>
<td>2.42</td>
</tr>
<tr>
<td>Total</td>
<td>N=148</td>
<td>28/94 (30%)</td>
<td>rtPA</td>
<td>10/119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin (4%)</td>
<td></td>
<td>(8%)</td>
</tr>
</tbody>
</table>

Relative Risk (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>rtPA-Heparin</th>
<th>rtPA</th>
<th>rtPA-Heparin</th>
<th>rtPA-Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.1 (2.2-29.6)</td>
<td>1.6 (0.4-6.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.a. = not applicable because percentage clot lysis is not reported. T=Thrombolysis, H=Heparin

A significant increase of clot lysis in those patients receiving fibrinolytic therapy (RR 8.1, 95% CI: 2.2-29.6), which is accompanied by an (insignificant) increased risk of major bleeding (RR 1.6 (95% CI: 0.4-6.4). Pulmonary embolism was not observed in these studies. Finally, there are two trials comparing urokinase with unfractionated heparin101. In the first study, 250,000 U urokinase as a bolus was administered followed by 750,000 U over 25 minutes, while in the other study 200,000 U urokinase over 24 hours was given. Based on a total of 37 patients, these studies showed non-significant differences in venographic efficacy and safety.

Taken together, the results of all studies show a similar picture in that early efficacy in terms of vein patency is better in patients treated with fibrinolytics as compared with unfractionated heparin. However, it remains unproven that this better venographic vein patency rate results in a lower risk of the post-thrombotic syndrome. Moreover, the price to be paid is a much higher risk for major bleeding. Therefore, fibrinolytic therapy for deep vein thrombosis should not be applied unless in the setting of a clinical study to assess the real value in the prevention of the post-thrombotic syndrome.

**Catheter directed fibrinolytic therapy**

Catheter directed fibrinolytic therapy involves administration of the fibrinolytic agent directly at the site of the thrombus using a catheter. Many access routes have been used, such as the internal jugular vein, contralateral femoral vein as well as the ipsilateral femoral or popliteal vein. Initially, urokinase has been used and more recently r-tPA. There are no randomized trials comparing catheter-directed
fibrinolytic therapy with standard anticoagulant therapy for deep vein thrombosis. Recently, a review describing several case-reports and case-series has been published. In this review 263 patients were treated with catheter directed fibrinolytics for iliofemoral or caval vein thrombosis. A total of 221 (84%) of the patients had a good short-term outcome in terms of vein patency and 4.9% suffered from major bleeding. Long-term outcome was not reported. Also the results of an American multi-center registry of patients treated with catheter-directed fibrinolytic therapy has recently been published. In this registry, data of 473 patients treated with catheter directed fibrinolytics were recorded. After one week only 287 (61%) patients could be analysed. Venous patency rates were 83% in the first week, but after 6 months 65% and after 12 months 60%. This is comparable with the standard treatment with LMWH and vitamin K antagonists. Major bleeding occurred in 16% of the patients and 0.4% of the patients died as a direct result of the fibrinolytic therapy. Therefore, based on these data, the role for catheter-directed fibrinolytic therapy is limited and the benefits are unproven. Possibly the only exception is a severe clinical presentation of deep vein thrombosis such as phlegmasia coerulea dolens.

**Pulmonary embolism**

**Background - epidemiology, natural history and prognosis**

Pulmonary embolism involves an occlusion of one or more pulmonary arteries by material originating from outside the pulmonary circulation, usually the deep leg veins. Symptoms of pulmonary embolism include shortness of breath, pleuritic chest pain, hemoptysis, and sometimes syncope. These symptoms are not specific: after objective testing with imaging techniques such as ventilation perfusion scintigraphy and pulmonary angiography, the disease is confirmed in only 20-30% of patients presenting with a suspicion of pulmonary embolism. Pulmonary embolism is a relatively frequently occurring disease: the estimated annual incidence is about 1-2 per 1000 inhabitants in the Western world. However it is difficult to estimate the real incidence of pulmonary embolism since many cases are unrecognised, as revealed by autopsy studies.

Based on reports from the mid-twentieth century, the mortality rate of untreated pulmonary embolism seems to vary around 25%. It has to be noticed that at that time the diagnosis was based on a combination of symptoms and signs and information from chest X-ray and electrocardiogram. Since Barritt and Jordan reported their landmark randomised controlled trial in 1960 of anticoagulants (a combination of vitamin K antagonists and heparin) versus no treatment, anticoagulant therapy has become standard in the management of pulmonary embolism. The trial stopped prematurely after 35 patients had been included because in the 19 untreated patients 5 died of pulmonary embolism and 5 other patients developed non-fatal recurrences, whereas in the 16 treated patients only 1 patient died due to
another reason. Although survival has improved considerably with adequate anticoagulant treatment, the pulmonary embolism-related mortality rates in the first 3 to 6 months remain 3% to 7%. Hence, there is room for more effective therapeutic modalities.

Anticoagulant treatment - heparin and vitamin K antagonists
Standard anticoagulant therapy for patients with acute pulmonary embolism consists of unfractionated heparin (UFH) followed by vitamin K antagonists. UFH is given by intravenous pump infusion for at least five days in a dose that is adjusted to prolong the activated partial thromboplastin time 1.5 - 2.5 times the normal range. Vitamin K antagonists are started with UFH and can be discontinued when the INR is in the therapeutic range (2.0 to 3.0) for two consecutive days. Patients with a first episode of PE should be treated for at least 3 months. The principal aims of this treatment are to prevent thrombus extension and the occurrence of new pulmonary emboli with a minimal risk of bleeding. Two large clinical studies have shown that low molecular weight heparins (LMWH) are as effective and safe as UFH for the initial treatment of pulmonary embolism. Because the total amount of patients studied is much smaller as compared to that for the treatment of DVT, UFH remains the standard therapy for patients with acute pulmonary embolism, although LMWH is a good alternative.

Fibrinolytic therapy
Fibrinolytic therapy has been investigated as the initial treatment in patients with acute pulmonary embolism for many years. The rationale for the use of fibrinolytic therapy is based on the expected more rapid thrombus resolution compared to heparin therapy alone. As a result, lung perfusion will be restored more quickly with a potential clinical benefit. Moreover, right ventricular overload could be decreased which might prevent right ventricular failure, systemic hypotension, shock and ultimately death. Also long-term clinical benefit could theoretically be achieved by preventing chronic right ventricular dysfunction and pulmonary hypertension. Lastly, recurrences of pulmonary embolism could be prevented because of the more complete resolution of the source of emboli.

Efficacy of fibrinolytic therapy - surrogate markers
The theory that pulmonary perfusion will be more rapidly restored by fibrinolytic therapy (‘thrombolysis’) is supported by several clinical reports. In a study with 36 selected patients treated with rtPA, 34 of the 36 patients showed thrombus resolution as assessed by follow-up angiography after 2 to 6 hours. Comparison with heparin is possible in the randomised controlled UPET, PIOPED, and PAIMS-2 trials, which showed more thrombus resolution 2 hours after thrombolysis as compared with heparin therapy. Table 3 summarizes the effects in the different studies of
thrombolysis as compared to heparin alone with respect to scintigraphic thrombus resolution. After 24 hours significant differences in thrombus resolution exist in favour of thrombolysis. However, when lung perfusion is compared in a later stage – i.e. after 7 days, 30 days and 1 year – these differences are no longer detectable.

When right ventricular function is considered as an outcome measure for the efficacy of fibrinolytic treatment the same pattern is observed. Short-term improvement of right ventricular function is achieved in patients receiving fibrinolytic treatment. In a study with 7 patients receiving rtPA, right ventricular wall movement normalised in 5 patients and improved in 2. In a non-randomised prospective trial of 40 patients with major PE receiving heparin (13 patients) or rtPA (27 patients), signs of echocardiographic right ventricular overload (such as right ventricular dilatation, paradoxal septal movement, inspiratory collapse of the vena cava) were significantly less after 12 hours in the group treated with rtPA, as compared with heparin recipients. One randomised trial evaluated right ventricular function in patients who received either alteplase or heparin. After 3 hours, improvement of right ventricular wall motion occurred in 29% in patients receiving rtPA, whereas

\[
\text{Table 3. Lung scintigraphic thrombus resolution after thrombolysis and heparin as compared with heparin alone}
\]

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimen</th>
<th>Scintigraphic thrombus resolution (relative difference in not perfused lung proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>t=24 hours</td>
</tr>
<tr>
<td>UPEI 1970</td>
<td>Urokinase 4400 U/kg - 4400 U/kg/h for 12 h + Heparin</td>
<td>T-H H 22%  8%  41%  36%*  71%  73%*</td>
</tr>
<tr>
<td></td>
<td>Heparin N=70</td>
<td>T+H H 41%*</td>
</tr>
<tr>
<td>Levine 1990</td>
<td>rtPA 0.6 mg kg 2 min + Heparin</td>
<td>T-H H 37%  19%  58%  49%*</td>
</tr>
<tr>
<td></td>
<td>Heparin N=25</td>
<td>T+H H 51%*</td>
</tr>
<tr>
<td>PIOPED 1990</td>
<td>rtPA 40-80 mg 40-90 min</td>
<td>T-H H 26%  0%*</td>
</tr>
<tr>
<td></td>
<td>rtPA + Heparin N=4</td>
<td>T+H H 51%*</td>
</tr>
<tr>
<td>PAIMS-2 1992</td>
<td>100 mg  2 h rtPA + Heparin</td>
<td>T-H H 37%  17%*</td>
</tr>
<tr>
<td></td>
<td>Heparin N=16</td>
<td>T+H H 54%  17%*</td>
</tr>
<tr>
<td></td>
<td>rtPA + Heparin N=55</td>
<td>T-H H 68%*</td>
</tr>
</tbody>
</table>

*=differences not statistically significant, T=Thrombolysis, H=Heparin
Fibrinolytic therapy in venous thromboembolism

it improved in 13% of the heparin recipients. After 24 hours these figures where 39% and 17%, respectively. However in the study of Konstantinides et al. the signs of acute right ventricular pressure overload progressively resolved at follow-up echocardiography after 48 hours and 7 days, regardless of the type of treatment. Taken together, these results suggest that thrombolysis induces early reperfusion of lung tissue and improvement of right ventricular function, an effect which can also be attained by heparin alone, albeit at a slower pace.

Efficacy of fibrinolytic therapy - clinical outcomes

How do these findings on surrogate markers translate into clinical outcomes? The largest clinical trial of thrombolysis versus heparin is the UPET trial, reported in 1970. In this trial, 82 patients were randomised to urokinase followed by heparin whereas the other 78 patients received heparin alone. In the urokinase group, 6 patients developed a PE recurrence (of which 1 episode was fatal) and 6 patients died. In the heparin group, 5 patients had a PE recurrence and 7 patients died. Thus, no clear differences were observed between the two treatment groups in clinical outcome. Since 1990, several randomised trials comparing the fibrinolytic agent recombinant tissue plasminogen activator (rtPA) to heparin alone have been conducted using different dosing regimens. The findings of these studies are detailed in Table 4. No significant differences in VTE recurrences and mortality could be observed, although the sample sizes of the individual studies were small. Patients treated with heparin have a 1.3 times higher risk regarding all cause mortality than patients receiving thrombolysis, however this result is not statistically significant. Although neither statistically significant, there appears to be a beneficial effect of thrombolysis as compared to heparin with respect to PE related mortality and VTE recurrences (relative risk of 1.6, 95% confidence interval: 0.5-5.3 and 1.4, 95% confidence interval: 0.6-3.3, respectively). In conclusion, there are no significant differences in clinical outcomes between the two treatment groups during the in-hospital observational period. According to the UPET study, also the 6-month mortality rates between patients treated with thrombolysis and heparin are comparable.

Safety-bleedings

It is well known that serious bleeding can occur with the use of fibrinolytic therapy. Levine et al reported an incidence of major haemorrhage of 8.4% and an incidence of fatal haemorrhage of 2.2%, based on 227 patients treated with rtPA (50-100 mg). When intracranial haemorrhages are considered, incidence rates vary from 1.5% to 3% When the incidence of bleedings is analysed in the 6 randomised trials (Table 5), significant differences are observed between
thrombolysis and heparin. The rate of major bleedings is higher in the thrombolysis (14%) than in heparin (7%) treatment group (RR 1.8, 95% CI: 1.04 - 3.1). In addition, there is a significant 4-fold higher risk of minor bleedings in patients receiving thrombolysis as compared to heparin recipients. Although all studies included in the pooled analysis are randomised trials concerning patients with

Table 4. The short term (in-hospital) efficacy of thrombolysis and heparin versus heparin alone for the initial treatment of acute pulmonary embolism as assessed by clinical outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Treatment regimens</th>
<th>All-cause mortality</th>
<th>PE-related mortality</th>
<th>Recurrent VTE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPEI 1970</td>
<td>160</td>
<td>Thrombolysis 4400 U/kg + 4400 U/kg h for 12 h - Heparin</td>
<td>Heparin</td>
<td>1.53</td>
<td>0.25</td>
</tr>
<tr>
<td>Levine 1990</td>
<td>58</td>
<td>rtPA-Heparin</td>
<td>Heparin</td>
<td>1.20</td>
<td>1.16</td>
</tr>
<tr>
<td>PIOPEH 1990</td>
<td>13</td>
<td>rtPA-Heparin</td>
<td>Heparin</td>
<td>1.14</td>
<td>2.11</td>
</tr>
<tr>
<td>PAIMS-2 1992</td>
<td>36</td>
<td>rtPA-Heparin</td>
<td>Heparin</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Thierry 1978</td>
<td>25</td>
<td>Streptokinase 250000 IU/20 min-100000 IU/hour for 72 h - Heparin</td>
<td>Heparin</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Marini 1988</td>
<td>30</td>
<td>rtPA-Heparin</td>
<td>Heparin</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Goldhaber 1993</td>
<td>101</td>
<td>rtPA-Heparin</td>
<td>Heparin</td>
<td>0.46</td>
<td>2.55</td>
</tr>
<tr>
<td>Pooled Relative Risk (95% CI)</td>
<td>1.3 in favor of thrombolysis</td>
<td>1.7 in favor of thrombolysis</td>
<td>1.4 in favor of thrombolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.25</td>
<td>(0.6-2.5)</td>
<td>(0.6-5.0)</td>
<td>(0.6-3.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Including fatal pulmonary embolism
Table 5. The safety of thrombolysis and heparin versus heparin alone for the initial treatment of acute pulmonary embolism

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Treatment regimen</th>
<th>Major bleedings</th>
<th>Intracranial bleedings</th>
<th>Minor bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T. H</td>
<td></td>
<td>T. H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>UPET 1970</td>
<td>160</td>
<td>Urokinase + Heparin</td>
<td>22 82</td>
<td>11 78</td>
<td>0.82</td>
</tr>
<tr>
<td>Levine 1990</td>
<td>58</td>
<td>rtPA + Heparin</td>
<td>0.33</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>PIOPE D 1990</td>
<td>13</td>
<td>40-80 mg-40-90 min</td>
<td>1 9</td>
<td>0 4</td>
<td>0.9</td>
</tr>
<tr>
<td>PAIMS-2 1992</td>
<td>36</td>
<td>rtPA + Heparin</td>
<td>3 20</td>
<td>1 16</td>
<td>11 20</td>
</tr>
<tr>
<td>Ly 1978</td>
<td>25</td>
<td>Streptokinase</td>
<td>4 41</td>
<td>2 11</td>
<td></td>
</tr>
<tr>
<td>Goldhaber 1993</td>
<td>101</td>
<td>rtPA + Heparin</td>
<td>1 46</td>
<td>0 55</td>
<td>3 46</td>
</tr>
<tr>
<td>Total</td>
<td>368</td>
<td>Thrombolysis + Heparin</td>
<td>31 204</td>
<td>15 189</td>
<td></td>
</tr>
</tbody>
</table>

Pooled Relative Risk (95% CI) | 1.8 (1.04-3.1) | 2.4 (0.1-55.9) | 4.0 (1.8-90.0) |
Test for heterogeneity | p=0.98 | NA | p=0.26 |

+: no exact data available, T=Thrombolysis, H=Heparin, NA=not applicable

confirmed pulmonary embolism, the small numbers of patients in the individual studies and the difference in agents and dose regimens used limits the conclusion of the pooled results and warrants for careful interpretations. Nevertheless, the following conclusions can be drawn. Although there are short term positive findings with surrogate markers in patients treated with fibrinolytic treatments as compared to patients treated with heparin alone, no clear long-term benefits are observed in surrogate markers. When clinical outcome measures such as recurrent venous thromboembolism and mortality are concerned, a trend is seen favouring treatment with thrombolysis, however these results are by far not statistically significant. Together with the significantly increased bleeding risk in patients treated with thrombolysis, fibrinolytic therapy is not considered to be routinely indicated in patients with acute pulmonary embolism.
**Massive pulmonary embolism**

As described above, there is no role for fibrinolytic therapy in the standard treatment of patients with acute pulmonary embolism. Massive pulmonary embolism with hemodynamic instability is considered to be the only indication for fibrinolytic treatment. Besides non controlled observations, the only available evidence for this indication is based on a prematurely stopped randomised study by Jerjes-Sanchez et al in which 4 of the 4 patients who received heparin died, whereas 4 of the 4 patients allocated to thrombolysis all survived.

**Right ventricular dysfunction**

Some reports suggest an expansion of the indication for fibrinolytic therapy in patients with pulmonary embolism to those with ‘impending hemodynamic instability’ i.e patients with adequate blood pressures but who have echocardiographic signs of right ventricular dysfunction. About 30-40% of the patients presenting with pulmonary embolism have right ventricular dysfunction. In-hospital as well as long term (up to one year) mortality seems to be increased in these patients. Ribeiro et al. and Kasper and colleagues showed that right ventricular dysfunction is associated with a more than three fold increase in in-hospital as well as one-year total mortality. Another recent study showed an increase in pulmonary embolism-related in-hospital mortality between patients with echocardiographic right ventricular dysfunction (5%, 95% CI: 0-13%) as compared to those without (0%, 95% CI: 0-4%). To reduce the increased mortality rate in pulmonary embolism patients with echocardiographic right ventricular dysfunction, this subset of patients might benefit from more intensive treatment such as thrombolysis. Thusfar, only two non randomised trials have compared the mortality in hemodynamically stable patients with echocardiographic signs of right ventricular overload receiving thrombolysis and heparin to those receiving heparin alone. In the first study a 30-day mortality rate of 4.7% was observed in the thrombolysis group compared with 11.1% in the heparin group (p=0.16). On the contrary, in the other study, 4% of the patients in the thrombolysis group died versus 0 percent in the heparin group (p=0.12). The percentage of recurrent pulmonary embolism in both groups were similar, however the frequency of serious bleedings in the thrombolysis group (9.4%) significantly exceeded that in the heparin group (0%). Since these registry data are far from conclusive, the question whether to treat hemodynamically stable patients with echocardiographic signs of RV overload with fibrinolytics remains unresolved and needs urgently to be addressed in a proper randomised study.

**Dose regimen**

A task force committee for guidelines on diagnosis and management of acute pulmonary embolism...
listed all the relevant issues regarding the question which drug or dose regimen is to be preferred. With respect to differences in clinical outcome between the various regimens, no difference in mortality was found between rtPA, streptokinase or urokinase. However, differences exist in early hemodynamic improvement and bleeding. A 2-hour infusion of 100 mg rtPA achieves more rapid lysis than urokinase (4400IU/kg/h) during 12 to 24 hour: 0.6 mg/kg/15 min rtPA and 1.5 million IU streptokinase/2 hour. However, the difference between 100 mg rtPA/2 hour; 0.6 mg/kg/15 min and streptokinase/2 hour is limited to the first hour. Major bleeding complications occurred in 28% of the patients receiving urokinase in 12 h.; in 21% to 24% in patients receiving 100 mg of rtPA and in 11% of patients receiving 0.6 mg/kg rtPA. However, these differences did not reach statistical significance. Thus, no conclusive answer is available to the question which drug must be preferred for the treatment of patients with massive pulmonary embolism. The task force committee suggests that faster haemodynamic improvement may be relevant in the sickest patients, whereas the low incidence of bleeding observed with the 0.6 mg/kg rtPA bolus injection may be useful in patients with relative contraindications. Goldhaber argues that streptokinase instead of rtPA might be the preferred drug since large studies in patients with myocardial infarction showed that the risk of intracranial bleeding appears to be lower in patients treated with 1500000 U of streptokinase as compared to patients receiving rtPA.

**Summary and practical guidelines**

- There is no indication for fibrinolytic therapy in patients with deep vein thrombosis
- The indication for fibrinolytic therapy in patients with pulmonary embolism is limited to those patients with massive pulmonary embolism, accompanied with hypotension and/or shock.
- The following drug and dose regimens can be used:
  1. rtPA 100 mg in 2 hours
  2. Urokinase 4400 U/kg (loading dose over 10 min), followed by 4400 U/h for 12-24 h.
  3. Streptokinase 250,000 U (loading dose over 30 min), then 100,000 U/h for 24 h
- Fibrinolytic therapy should be instituted after objective testing, i.e. high probability scintigraphy, abnormal spiral CT or angiography; or in case of a high clinical suspicion combined with evidence of acute cor pulmonale (e.g. shown by echocardiography)
- The use of fibrinolytic therapy in patients with sub-massive pulmonary embolism (right ventricular dysfunction) is controversial
- Patients without massive pulmonary embolism should be treated with unfractionated heparin (or low molecular weight heparin). Unfractionated heparin should be started with a loading dose of
5000 U, followed by continuous infusion of 1250 U/h. Frequent measurements of aPTT are required to prolong the aPTT 1.5 - 2.5 times the normal range. The duration of treatment is at least 5 days and can be stopped when the INR is two times above 2.

- In all patients with vitamin K antagonists is indicated for at least 3 months. Therapeutic treatment aims at an INR between 2 and 3.

References


47. Goldhaber SZ. Thrombolysis in pulmonary embolism: a large-scale clinical trial is overdue. Circulation 2001; 104:2876-78.


