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Efficacy and safety of thrombolytic therapy in pulmonary thromboembolism

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POINTS OF INTEREST

- According to angiographical, gammagraphical, haemodynamic or ultrasound measures thrombolytic agents promote the resolution of the clot. However, this effect disappears 24-72 hours after the start of the treatment.
- Thrombolytic agents have not been found to reduce neither mortality nor relapses in pulmonary thromboembolism (PTE) patients.
- PTE patients treated with thrombolytic agents show a 2.6 fold increase in bleeding than patients not receiving this type of therapy.
- There is uncertainty on some aspects of the thrombolytic therapy in PTE, e.g. its mid and long term efficacy or its efficacy in subpopulations of more precisely selected patients.

DESCRIPTION OF THE DISEASE

PTE results from the impact in the pulmonary arterial tree of a clot detached from the venous territory.

Epidemiology and clinical course

The relevance of PTE is due to its high relative frequency in hospital patients, and to its potentially serious consequences. The incidence of confirmed PTE is estimated in at least 23 cases per 100,000 inhabitants/year, and intrahospital mortality rate is around 12%.[1] However, 25-30% of routine necropsies show old or recent pulmonary embolisms, although only 10-30% of these are diagnosed during the patient's life.[2-3] PTE incidence may be considered high if we consider that in most cases this condition may be prevented.[4-5]

In Catalonia, mortality rate due to this cause has been slightly but steadily decreasing from 1991 to 1995, according to the Catalan Mortality Register,[6] so that PTE mortality rate went from 5.3 cases/100,000 inhab./year in 1991 to 4.0 cases/100,000 inhab./year in 1995 (i.e., a total of 245 deaths in the latter year).

It is estimated that approximately 8% of the PTE patients suffered from relapses, nearly half of which died.[7] After one year, 23.8% of the patients has died. The main clinical conditions associated to these deaths are cancer, congestive heart failure and chronic pulmonary disease.

Treatment and prevention

The standard PTE therapy consists of the initial administration of heparin for 7-10 days to inhibit the clot growth, favour its resolution and prevent relapses; then oral anticoagulants are given during 3-6 months. Prevention of deep venous thrombosis and PTE with heparins, oral anticoagulants, dextran or platelet antiaggregants in high risk patients has shown clear benefits in decreasing mortality, morbidity, relapses and costs.[8-11] This fact shows the relevance of preventive treatment with anticoagulants in the reduction of the incidence of PTE and its associated mortality.

DESCRIPTION OF THE TECHNOLOGY

Thrombolytic agents are substances that degrade the intravascular clots or thrombi as a result of the activation of plasmin, an plasmatic enzyme that digests the fibrin that forms the clot. The objective of thrombolytic therapy is to restore the blood flow to preserve the pulmonary tissue and its functionality.

Currently available thrombolytic agents are streptokynase (SK), and urokynase (UR), called 'first generation', anisoylated plasminogen-streptokinase activator complex (APSAC), single chain urokinase plasminogen activator (SCU-PA) and recombinant tissue plasminogen activator (rt-PA).

DESCRIPTION OF THE PROBLEM

Heparin is an anticoagulant preventing the progression of the clot that does not act directly on already formed clots. Thrombolytic drugs were introduced to treat already existing thrombi. According to angiographical, gammagraphical, and/or haemodynamic measures, thrombolytic agents seem to degrade the clot more rapidly and completely than heparin, but with a higher risk of haemorrhage and a higher economic cost.[12-14] However, there still is uncertainty on the efficacy of thrombolytic therapy in PTE in terms of decreased mortality, prevention of relapses or improvement of the short, mid and long term quality of life.

OBJECTIVES AND METHOD

To contribute to ascertain the real value of thrombolytic therapy in PTE, a meta-analysis of randomised clinical trials comparing the efficacy and safety of this type of treatment with conventional ones with heparin in PTE patients has been undertaken (RCTs show a higher degree of scientific evidence[15]). The specific objectives of the study are:

1. To determine the therapeutical effect of thrombolytic agents in the treatment of PTE in terms of mortality and relapses.

2. To measure the haemorrhage risk in PTE patients treated with thrombolytic agents.

3. To determine if specific conditions or groups of patients treated with thrombolytic agents show a greater benefit and/or a lower risk of haemorrhage.

To identify the studies, a bibliographic search in the MEDLINE, Embase, Current Contents, HealthSTAR and the Cochrane Library databases was carried out, comprising the period January 1985 - November 1997, as well as a manual reference search of the most relevant articles. Two evaluators independently and blindly extracted the data regarding the characteristics of the studies and their results, and appraised the methodological quality of the clinical trials according to Jadad's scale.[16]

The quantitative synthesis of the results of the different studies has been performed with Meta-Analyst® programme, both for the fixed effects model—which assumes interstudy homogeneity— and for the random effects model —which considers inter- and intrastudy variability. Results were presented as odds ratio with 95% confidence intervals.

RESULTS

Table 1 shows the main prognostic variables of the treatment groups compared among the 8 RCTs identified,[17-24] and Table 2 shows the different features of the studies assessed.

a. Qualitative synthesis

Except for Ly's study (1978), where angiographical differences are found three days after the start of the treatment, no study showed differences in the resolution of the thrombus among both treatment groups 24 hours after the start of the therapy.

This effect has been evidenced in six out of eight RCTs assessed, only in some haemodynamic, gammagraphical or arteriographical variables (outcome measures considered intermediate), but not in other final outcome measures, more relevant for prognosis.

b. Meta-analysis

Mortality

No statistically significant differences have been found between mortality rate of patients with PTE treated only with heparin and that of patients treated also with some type of thrombolytic drug. There are no differences either when comparing mortality rate of patients treated with thrombolytics with that of controls (heparin) if those treated with rt-PA and those treated with SK or UK are studied separately (see Figures 1-3).

Relapses

The meta-analytic study of the clinical trials identified has not shown any statistically significant association between the type of therapy received and the presence or not of angiographically and/or gammagraphically confirmed thromboembolic relapses (see Figure 4).

Haemorrhage

PTE patients receiving thrombolytic therapy show a 2.5 fold higher risk of suffering some type of haemorrhage than PTE patients not receiving it (OR = 2.6, CI 95%: 1.6-4.4). The results of the meta-analytic study regarding major bleeding[i] show a 1.87 OR (CI 95%: 0.97-3.61) (see Figure 5).

i Any retroperitoneal or intracraneal bleeding, any open bleeding leading to a serum haemoglobin value over 2 g/dl or any bleeding requiring transfusion of at least 2 RBC concentrates is considered a major haemorrhage.

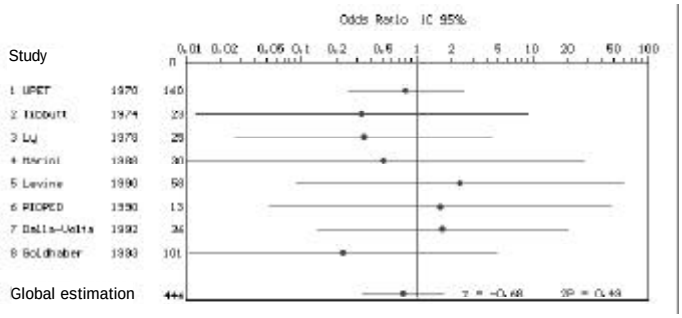

Figure 1. *Association between mortality and thrombolytic therapy in PTE patients considering any thrombolytic agent (results of the meta-analysis according to the random effects model).*

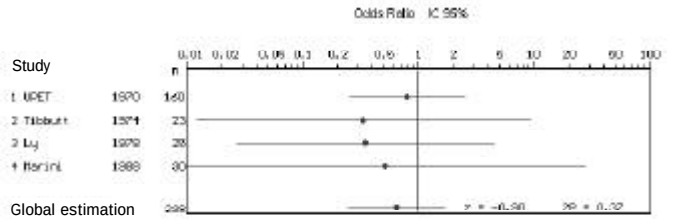

Figure 2. *Association between mortality and thrombolytic therapy in PTE patients considering only streptokynase and urokynase (results of the meta-analysis according to the random effects model).*

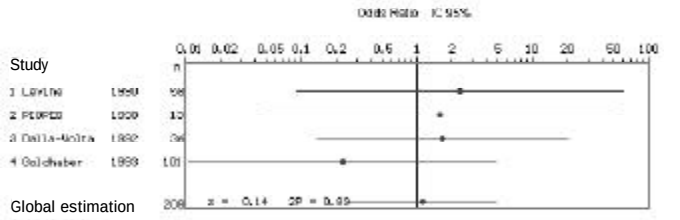

Figure 3. *Association between mortality and thrombolytic therapy in PTE patients considering only recombinant tissue plasminogen activator (results of the meta-analysis according to the random effects model).*

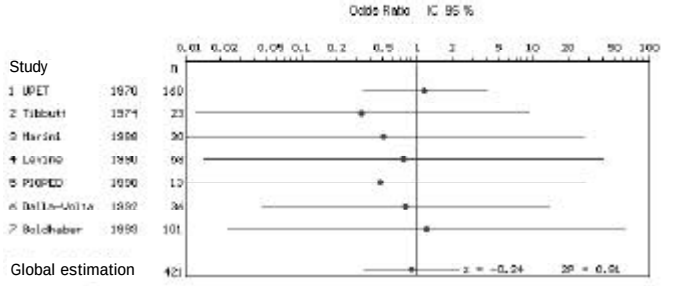

Figure 4. *Association between confirmed relapse of PTE and thrombolytic therapy (results of the meta-analysis according to the random effects model).*

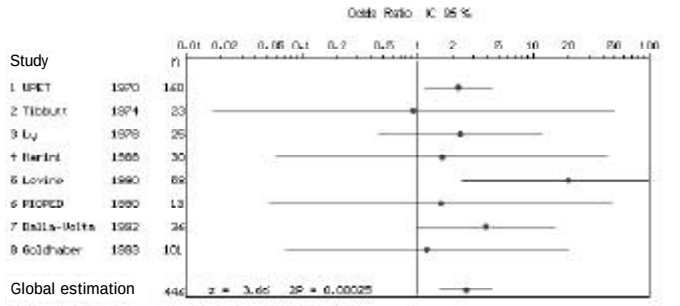

Figure 5. *Association between the risk of bleeding and thrombolytic therapy in PTE patients when considering all thrombolytic agents (results of the meta-analysis according to the random effects model).*

If the studies using SK or UK are considered independently from those using rt-PA, in both cases the risk of haemorrhage is found to be significantly higher than that of patients not receiving any type of thrombolytic treatment (see Figures 6 and 7).

The results of the meta-analysis carried out refer to the clinical outcomes observed during the patient's hospital stay and cannot be further extrapolated.

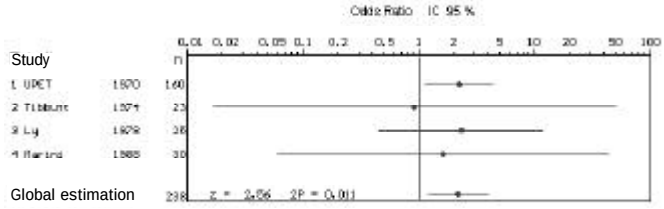

Figure 6. *Association between the risk of bleeding and thrombolytic therapy in PTE patients when considering only streptokynase and urokynase (results of the meta-analysis according to the random effects model).*

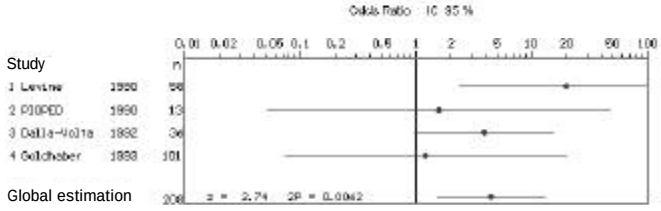

Figure 7. *Association between the risk of bleeding and thrombolytic therapy in PTE patients considering only recombinant tissue plasminogen activator (results of the meta-analysis according to the random effects model).*

FINAL CONSIDERATIONS

In general, and compared to other study fields of these particular drugs —e.g. myocardial infarction—, it may be considered that there are few RCTs assessing the efficacy and safety of thrombolytic agents in PTE. The assessed studies methodological quality, according to Jadad's[ii] scale criteria (randomisation, blinding and follow up losses), is low (average of 1.87 points, median 2 points, mode 1 point). Also, sample sizes of these studies are rather small, so that randomisation to a treatment group does not guarantee the strict comparability between treatment group and control group, statistical power is low and there is little precision in the estimation of the effect's magnitude.

It should be noted that the studies assessed consider a 4-day (approximately) window period —i.e. time between the onset of the symptoms and the start of the treatment. This period seems excessive, particularly if compared to the window period established for this sort of therapy in myocardial infarction (6 to 24 hours) or in acute brain infarction (3 to 6 hours).[25-26] The window period may be of great relevance in the efficacy of the therapy and in the patient's prognosis.

Thrombolytic agents seem to have an immediate effect that dilutes with time, probably due to the activation of physiological fibrinolysis. For this reason, thrombolytic agents may have an important role in massive PTE cases, with a higher haemodynamic involvement and more life threatening. Improvement of pulmonary blood pressure during the first hours found in the Dalla-Volta, Tibbutt and UPTE studies suggests further better results in this subgroup of PTE patients, mainly if administered in the earliest stages. However, this hypothesis is yet to be proven.

Haemorrhage risk in PTE patients treated with thrombolytics is approximately 20%, whereas the risk in patients randomised to the control group —treated only with heparin— is approximately 7%. That is, haemorrhage risk attributable to thrombolytic therapy and, therefore, avoidable if this therapeutical option was not selected, is 13%. It should be noted, however, that most of these haemorrhages were related to the insertion of catheters or other invasive procedures needed to obtain the efficacy measures established in the clinical trials assessed, but that may be avoided in everyday clinical practice.

[ii] Jadad's scale ranges from 0 to 5 points, so that the higher the score the better the methodological quality of the RCT.

Table 1. Pronostic variables of treatment groups to be compared in the evaluated clinical trials

STUDY	TREATMENT GRUPS (SAMPLE SIZE)	MEAN AGE (YEARS)	MAN/ WOMAN RATIO (% OF MEN)	DURATION OF SYMPTOMS PRIOR TO RANDOMISATION	EXPECTED PTE OR DVT	BASAL PERFUSION DEFFICIENCY (%)	LAST M.SURG. TRAUMA OR IMMOBIL.	PRESENCE OF CANCER
1.Goldhaber 1993	rt-PA (N=46) Hep. (N=55)	58 59	16/30 (34.8%) 28/27 (50.9%)	0-5/>5 d 34/10 0-5/>5 d 43/12	16/46 (34.8%) 22/55 (40%)	42.9 36.0	8/46 (17.4%) 4/55 (7.3%)	6/46 (13%) 4/55 (7.3%)
2. Levine 1990	rt-PA (N=33) Hep. (N=25)	61.5 59.6	18/15 (54.5%) 11/14 (44%)	5.9 days 5.6 days	7/33 (21.2%) 6/25 (24%)	27.4 21.3	n.a. n.a.	5/33 (15.1%) 8/25 (32%)
3. PIOPED 1990	rt-PA (N=9) Hep. (N=4)	57.7 60.0	5/4 (55.5%) 4/0 (100%)	<7 days (?) <7 days (?)	n.a. n.a.	39 41	n.a. n.a.	n.a. n.a.
4.Dalla-Volta 1992	rt-PA (N=20) Hep. (N=16)	65.7 63.4	7/13 (35%) 5/11 (31.2%)	3.1 days 3.0 days	8/20 (40%) 5/16 (31.2%)	Miller basal=28.3 Miller basal=25.3	8/20 (40%) 2/16 (12.5%)	0/20 (0%) 3/16 (18.7%)
5. Marini 1988	UK (3 days)(N=10) UK (bolus)(N=10) Hep. (N=10)	52 60 47	5/5 (50%) 6/4 (60%) 7/3 (70%)	3.5 days 3.17 days 3.35 days	n.a. n.a. n.a.	num. seg. not perf.=13.6 num. seg. not perf.=13.8 num. seg. not perf.=13.0	n.a. n.a. n.a.	n.a. n.a. n.a.
6. UPET 1970	UK (N=82) Hep. (N=78)	<50/>=50 46/36 <50/>=50 35/43	47/35 (57.3%) 45/33 (57.7%)	n.a. n.a.	10/82 (12.2%) 9/78 (11.5%)	26.6 25.4	n.a. n.a.	n.a. n.a.
7. Tibbutt 1974	SK (N=13) Hep. (N=17)	51 47	4/9 (30.8%) 11/6 (64.7%)	n.a. n.a.	n.a. n.a.	Miller basal=21.9 Miller basal=18.6	10/13 (76.9%) 14/17 (82.3%)	0/13 (0%) 1/17 (5.9%)
8. Ly 1978	SK (N=14) Hep. (N=11)	51 56	8/6 (57.1%) 3/8 (27.3%)	0-2/>2 d 11/3 0-2/>2 d 7/4	9/14 (64.3%) 7/11 (63.6%)	Miller basal=21.6 Miller basal=18.1	5/14 (35.7%) 4/11 (36.4%)	1/14 (7.1%) 1/11(9.1%)

UK: streptokynase.
SK: urokynase.
Hep.: heparin.
DVT: deep venous thrombosis.
n.a.: not available
rt-PA: recombinant-tissue plasminogen activator

CONCLUSIONS

- There are few clinical trials addressing the efficacy and safety of thrombolytic therapy in PTE; overall, the methodological quality or rigour of the existing studies, according to Jadad's scale, is low. Also, studies published so far differ widely among each other, both regarding the efficacy measures used and the type of thrombolytic agent, used schedule and other features of the study.

- Six out of 8 clinical trials assessed show that during the first 24 hours thrombolytic agents improve some of the angiographical, gammagraphical, haemodynamic or ultrasonographic variables considered. However, 24-72 hours after the start of the therapy there are no differences in these efficacy measures among patients receiving thrombolytic therapy and those not receiving it.

- The results of the meta-analysis carried out show that there are no differences in mortality rate nor in the PTE confirmed relapses rate during the hospital stay among patients treated with thrombolytic agents and those who were not. Therefore, the efficacy of the treatment has not been proven in the most clinically relevant outcomes.

- The results of the meta-analysis also show that PTE patients treated with thrombolytic agents show a significantly higher haemorrhage risk than patients not receiving this treatment. However, most of these are minor haemorrhages related to the patients management (mainly insertion of the catheter).

- There is little scientific evidence on the efficacy and effectiveness of thrombolytic therapy in PTE regarding the clinically relevant mid and long term outcomes, such as mortality, relapses, remaining dyspnea, tolerance to exercise or quality of life, and regarding the efficacy and effectiveness of this therapy in the subpopulation of haemodynamically unstable patients with massive PTE.

Table 2. Characteristics of the evaluated clinical trials

STUDY	EFFICACY MEASUREMENT AND FOLLOW-UP TIME	THERAPIES TO COMPARE	SCHEDULE OF THE COMPARED THERAPIES
1. Goldhaber 1993	Ultrasonography: basal, 3 and 24h Gammagraphy: basal and 24h Clinical follow-up: between 14 and 21 day	rt-PA + Hep. vs. Hep.	rt-PA: 50 mg iv/h for 2h (100 mg iv/2h) + Hep: 1000 U/h for 5 days Hep: 5,000 U bolus + 1,000 U/h for 5 days
2. Levine 1990	Gammagraphy: basal, 24h and 7th day Clinical follow-up: up to 10th day	rt-PA + Hep. vs. Hep.	rt-PA: 0.6 mg/kg bolus + Hep: 5,000 U bolus + 30,000 U/24h +continuous iv infusionmonitorised with PTT Hep: 5,000 U bolus+ 30,000 U/24h +continuous iv infusion monitorised with PTT
3. PIOPED 1990	Arteriography: basal and 2h. Gammagraphy: basal, 24h, 48h and 7th day Hemodynamics: basal and 1.5 h	rt-PA + Hep. vs. Hep.	rt-PA: 40-80 mg iv (1mg/min) + Hep (schedule n.a.) Hep (schedule n.a.)
4. Dalla-Volta 1992	Arteriography: basal and 2 h Gammagraphy: basal, 7th and 30th day	rt-PA + Hep. vs. Hep.	rt-PA: 100 mg iv/2h + Hep: 10,000 U bolus + continuous iv infusion monitorised with PTT Hep: 10,000 U bolus + continuous iv infusion monitorised with PTT
5. Marini 1988	Gammagraphy: basal, 24h. 3rd, 7th and 30th day, and 6 and 12 months Arteriography: basal and 7th day PAP: basal and 7th day PaO2: basal, 24h, 3rd, 7th and 30th day and 6 and 12 months. Arteriography: basal and 7th day	UK vs Hep.	UK: 800,000 U iv/day for 3 days UK: 3,300,000 U iv/12h Hep: 30,000 U iv/day for 7 days
6. UPET 1970	Arteriography: basal and 24h. Gammagraphy: basal, 1st, 2n 5th and 14th day, and 3. 6 and 12 months. Hemodynamics: basal and 24h	UK + Hep. vs Hep.	UK: 4.350 U/kg bolus + 4.350 U/kg/h cont. iv inf. for 12h + Hep: ? iv 5 days Hep: 165 U/kg bolus + 22U/Kg/h continuous iv infusion for 12h + ? iv 5 days
7. Tibbutt 1974	Arteriography and hemodynamics: basal and 3rd day (72h)	SK vs Hep.	SK: 600,000 U/30 min + 100,000 U/h continuous iv infusion for 3 days Hep: 5,000 U/30 min + 2,500 U/h continuous iv infusion for 3 days
8. Ly 1978	Arteriography: basal and 3rd day	Sk vs. Hep.	SK: 250,000 U bolus + 100,000 U/h continuous iv infusion for 3days Hep: 15,000 U bolus + 30,000 U/day continuous iv infusion (7 days)

Follow-up therapies with oral anticoagulants no corticoid solutions, etc for the minimisations of secondary effects have not been considered.

UK: streptokynase.

SK: urokynase.

Hep.: heparin.

rt-PA: recombinant-tissue plasminogen activator.

n.a.: not available

RECOMMENDATIONS

- Thrombolytic therapy in PTE has not been found to reduce short term mortality or relapses, its long term effects are unknown and, however, it is clearly associated to a higher risk of haemorrhage. Therefore its routine use in everyday clinical practice is not advised.

- The use of thrombolytic agents in PTE should be limited to rigorous experimental studies of quality, based on pathophysiologically plausible hypotheses, oriented to solve the remaining uncertainties of the efficacy of this treatment compared to standard treatment in the target population or subpopulation.

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