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Title: Effect of prolonged intra-aortic balloon pumping in patients with cardiogenic shock following acute myocardial infarction

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Abstract: Objectives: To evaluate the efficacy of prolonged intra-aortic balloon pumping (IABP) support in patients with cardiogenic shock following acute myocardial infarction (AMI).Methods: Thirty-nine patients with cardiogenic shock after AMI were treated with percutaneous coronary intervention which was supported by IABP. After 72 hours of IABP, the patients who attained the criteria of IABP withdrawal were randomly divided into two groups. The control group ceased IABP whereas the study group continued IABP for additional seven days.Results: After IABP, mean arterial pressure, cardiac index, left ventricle ejection fraction and arterial oxygen saturation were significantly elevated in all patients whereas pulmonary capillary wedge pressure and heart rate were decreased. The improvement of cardiac index, left ventricular ejection fraction and pulmonary capillary wedge pressure in the study group was greater than the control group ($P<0.05$). After 12-month follow-up, the 6-min walking test and left ventricular ejection fraction in the study group were significantly higher than those of the control group ($P<0.05$). No significant differences were noted between the two groups in the incidence ventricular aneurysm and mortality rate.Conclusion: Prolonged use of IABP for up to 10 days offers additional long term benefit in left ventricular function and exercise tolerance.

Thrombolytic therapy for pulmonary embolism in patients with stable haemodynamics

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Summary

Background. The use of thrombolytic agents in the treatment of haemodynamically stable patients with pulmonary hypertension remains uncertain.

Patients and Methods. Urokinase (20,000 IU /kg) was intravenously administered to 36 patients who had pulmonary embolism and a normal blood pressure. This was followed by subcutaneous injection of a low-molecular-weight heparin for a week.

Results. Improvement in clinical symptoms and reduction in pulmonary pressure was observed in 28 (77.8%) patients within the first week of the thrombolytic therapy. The improvement rate in patients with embolic symptoms of less than 14 days, and in those who had symptoms between 14 and 30 days before the thrombolytic therapy was 86% and 50%, respectively ($p < 0.01$). Non-life threatening bleeding complications were observed in 10 (22.2%) patients.

Conclusions. Thrombolytic therapy with urokinase followed by low-molecular-weight heparin is an effective therapeutic strategy for patients with pulmonary embolism and stable haemodynamics. However, the long-term benefits of this strategy remains to be seen.

Key words: pulmonary embolism, urokinase, thrombolytic therapy, low molecular weight heparin.

Introduction

Pulmonary embolism is a medical emergency and is associated with significant morbidity and mortality. It often leads to pulmonary hypertension and right-sided heart failure. Patients with right ventricular dysfunction due to pulmonary embolism had increased rates of in-hospital death, even in the absence of arterial hypotension or shock [1, 2].

Anticoagulation remains the mainstream of treatment for pulmonary embolism. The primary aims of anticoagulation therapy are to diminish the propagation of the existing thrombus and to prevent recurrent embolism. Thrombolysis is an established treatment for patients with acute massive pulmonary embolism and haemodynamic instability or cardiogenic shock [3]. A recent clinical trial has indicated that thrombolysis may also benefit patients with submassive pulmonary embolism and relative stable blood pressure [4].

The primary aim of the present study is to evaluate the short-term effect of thrombolytic therapy on patients with pulmonary embolism and stable haemodynamics.

Patients and Methods

Patient selection

The study was approved by the Institutional Review Board of the First Teaching Hospital of Zhengzhou University. Consent was obtained from all patients in the study. Between July 2000 and July 2005, thrombolytic therapy with urokinase was performed in a selected group of patients who admitted into the hospital with a diagnosis of pulmonary embolism.

The selection criteria were clinical symptoms suggesting pulmonary embolism and positive results from all the following laboratory tests: 1) pulmonary embolism confirmed by pulmonary angiography, ventilation-perfusion lung scanning; 2) echocardiographically-detected pulmonary

hypertension, right ventricular enlargement, and tricuspid regurgitant jet velocity greater than 2.8 m/sec (4).

Patients were excluded from the study if they had one or more of the following characteristics: 1) more than 70 years; 2) massive pulmonary embolism involving more than three lung segments; 3) persistent arterial hypotension with or without signs of cardiogenic shock; 4) onset of symptoms more than 30 days; 5) a history of major surgery, trauma, or stroke within the preceding three months; 6) major bleeding within the preceding 14 days.

Thrombolytic therapy

Before the administration of thrombolytic drug, the following laboratory tests were conducted: full blood count; blood biochemistry profile; prothrombin time (PT); activated partial thromboplastin time (APTT); partial pressure of oxygen in the arterial blood (PaO₂); partial pressure of carbon dioxide in the arterial blood (PaCO₂); ECG; and echocardiographic measurement of pulmonary systolic pressure.

Urokinase (20,000 IU/kg) was intravenously infused in 0.9% normal saline over 2 hours. This was followed by subcutaneous injection of a low-molecular-weight heparin (dalteparin, 4,100 U) every 12 hours for seven days. Warfarin was commenced 2 days before the cessation of dalteparin and continued as maintenance anticoagulation therapy for 6 months.

Assessment of clinical response

Patients were evaluated at day 1, 3 and 7 after urokinase infusion. Effective therapy was defined by the presence of all of the following characteristics: 1) improvement in clinical symptoms, particularly dyspnea; 2) reduction of pulmonary pressure by 10 mm Hg or more; and

3) a reduction in the deficient lung segment on ventilation-perfusion lung scanning by 0.25 or more.

Statistical analysis

Data were presented in means \pm SD. The differences before and after thrombolytic therapy were analyzed by student *t*- test. $P < 0.05$ was considered to be statistically significant.

Results

Effective rates

Effective responses were observed in 28 (78%) patients 7 days after the urokinase administration. The effective rate in patients with onset of symptoms less than 14 days before the thrombolytic therapy was 86% (24/28), whereas it was 50% (4/8) in those with symptoms of between 14-30 days ($p < 0.01$).

Effect of urokinase on clinical and laboratory characteristics (Table 1)

At day 7 of the thrombolytic therapy, there was a reduction in heart rate and respiration rate (Table 1, $p < 0.05$). There was also an improvement in the blood oxygen levels and a reduction in blood PH values in these patients (Table 1, $p < 0.05$). The pulmonary systolic pressure was reduced by an average of 22.5 mm Hg (Table 1, $p < 0.05$). APTT remained unchanged but PT and fibrinogen A were elevated (Table 1, $p < 0.05$).

Adverse effects

There was no fatal bleeding, such as hemorrhagic stroke, after the thrombolytic therapy.

However, subcutaneous bleeding (n=2), hematuria (n=2), nosebleed (n=2) and hemoptysis (n=2) were noted within 3 days of the urokinase administration. These adverse effects resolved spontaneously without specific medical intervention in the following 7 days before hospital discharge.

Discussion

The current standard treatment for pulmonary embolism is low-molecular-weight heparin or unfractionated heparin for at least 5 days, followed by warfarin for at least 3-6 months to prevent escalation of thromboembolism [5, 6]. Thrombolytic drugs such as urokinase, streptokinase or recombinant tissue plasminogen activator act by converting plasminogen to plasmin, which dissolves the thrombus. The rationale behind thrombolytic therapy is that, in conjunction with anticoagulation, it may reduce the rate of death, recurrent pulmonary embolism and pulmonary hypertension [7].

Several clinical trials compared the efficacy of thrombolysis and anticoagulation. Urokinase was found to be superior to unfractionated heparin in improving lung scans, pulmonary angiograms and right ventricular pressure 24 hours after the treatment [8]. However, lung scans performed 7 days, 14 days, 3 and 6 months after the treatment remained similar between the urokinase and heparin groups [8], suggesting thrombolytic therapy has limited long-term clinical benefits.

Further studies were conducted to evaluate the efficacy of combined treatment with thrombolysis and heparin. At 24 hours, a combination of urokinase and unfractionated heparin was superior to heparin alone in improving lung scans in patients with pulmonary embolism [9]. However, no significant differences were apparent between the two groups over a longer period of time [9].

Due to the lack of perceived long-term efficacy, thrombolysis has been mainly used for the management of massive pulmonary embolism, which is often accompanied by hypotension or cardiogenic shock [5, 10]. The use of thrombolytic therapy in patients with submassive pulmonary embolism and stable haemodynamics has long been debated and remains controversial. The Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism Trial 3, one of the largest trials in the field involving 256 patients, shows that, compared with heparin only treatment, alteplase (100 mg over 2 hours) plus heparin substantially reduces the need for intensive therapeutic measures such as mechanical ventilation, pressor agents or secondary thrombolysis during hospitalization [4]. The probability of 30-day event-free survival is higher in the heparin-plus-alteplase group [4].

Our self-controlled study included only a small number of patients who received urokinase plus a low-molecular-weight heparin. There was a clear improvement in clinical symptoms, pulmonary pressure, blood oxygen levels and ventilation-perfusion lung scanning 7 days after the treatment in nearly 80% of the patients. There was no fatal bleeding following the thrombolytic regimen, although minor bleeding occurred in approximately 22% of the patients.

Although urokinase, streptokinase and recombinant tissue plasminogen activators have been used to treat pulmonary embolism, the differences in therapeutic efficacy between them are not very clear. A study in the mid-70's found no significant difference in efficacy between urokinase and streptokinase [9]. Further studies by Goldhaber and associates [11] and the European Cooperative study [12] compared recombinant tissue plasminogen activators and urokinase and found that, although recombinant tissue plasminogen activators initially produced a faster resolution of the thrombus, results were the same after 24 hours.

Our study doesn't have a control (heparin treatment alone) group, which may make the

interpretation of the final therapeutic responses complicated; the favorable responses may be due to the pharmacological actions of urokinase, or dalteparin, or both. However, previous studies have clearly demonstrated the superior clinical effects of urokinase in the first few days of therapy in patients with massive pulmonary embolism and unstable haemodynamics [8, 9]. The present study doesn't intend to compare the therapeutic effects of urokinase and heparin in haemodynamically stable patients. Rather, it shows that the combination of urokinase and dalteparin offers significant clinical benefits in most of the patients receiving this regimen.

In conclusion, thrombolytic therapy together with low-molecular-weight heparin appears to be a safe and effective therapy for patients with pulmonary embolism and stable haemodynamics. This treatment improves clinical symptoms and reduces pulmonary pressure, diminishing the risk of right ventricular failure. However, the long-term effects of the thrombolytic therapy in such patients need further investigation.

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Table 1. Clinical and laboratory characteristics before and after thrombolytic therapy.

	Before (n=36)	After (n=36)	<i>P value</i>
Heart rate (beats/min)	91 ±18	69 ±12	< 0.05
Respiration rate (breaths/min)	25 ±7	18 ±6	< 0.05
SBP (mm Hg)	130.2±14.7	132.8±18.6	>0.05
DBP (mm Hg)	76.7±12.3	78.6±13.9	>0.05
Blood PH	7.46±0.03	7.31±0.02	< 0.05
PaO ₂ (mm Hg)	68.3±12.8	82.5±5.6	< 0.05
PaCO ₂ (mm Hg)	33.0±5.6	36.8±5.8	< 0.05
PSP (mm Hg)	71.3±18.0	48.8±14.3	< 0.05
PT (s)	12.3±0.8	18.3±1.5	<0.05
Fibrinogen A (g/L)	4.5±1.0	7.5±0.5	<0.05
APTT (s)	33.4±4.5	38.3±3.5	>0.05

SBP and DBP: systolic and diastolic pressure; PSP: pulmonary systolic pressure;

PT: Prothrombin time; APTT: activated partial thromboplastin time.