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The blood presure recovery–marker of haemodynamic instability improvement in patients with pulmonary embolism

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Abstract

The objective of the study is represented by the assessment of the post-thrombolysis blood pressure [BP] recovery in patients with intermediary-high risk pulmonary embolism [PE]. Method: We included 65 patients admitted in the Cardiology Department of Bagdasar Arseni Emergency Hospital. The inclusion criteria: a) first episode of acute PE; b) Both echocardiographic and biochemical markers of RV dysfunction present. Exclusion criteria: a) history of PE; b) age > 80 y.o.; c) cardiomyopathies with severe left ventricle [LV] dysfunction [LV ejection fraction [LVEF] < 35%]. The patients were divided in control group – 37 patients – [receiving anticoagulant therapy] and study group – 28 patients – [both thrombolytic and anticoagulant]. The haemodynamic instability was assessed on admission and on 7th day, the blood pressure recovery was evaluated by a medium of 10 blood pressure [BP] measurements on admission compared to automatic monitoring of BP on 24 hours from admission. Results: There were no differences regarding the sex distribution between the two groups and no statistical significant difference regarding the medium systolic BP [SBP] value on admission. We proved the significant lowering of the haemodynamic instability rate in the study group compared to control group [1:9.33 vs 1:3.8, p 0.03]. There was a statistical significant difference between the two groups regarding the systolic BP recovery on 24 hours after admission [increase of the medium SBP in study group with 17.99% vs 14.05%, p 0.04] and the double product [DP] value on 24 hours after admission [decrease of DP in study group 11.74% vs 8.6].

Keywords: Intermediary-high risk pulmonary embolism, thrombolysis, haemodynamic instability, blood pressure recovery, double product, medium systolic blood pressure.

Introduction

Intermediary – high risk PE represents the type of PE with no features of cardiogenic shock but with both echocardiographic signs of RV overload and biochemical markers of RV dysfunction , the patient's severity index being higher than 85 [PESI > 85] [1]. The intermediary risk PE is a heterogeneous medical condition regarding the mortality rate [early mortality (Mt) - 2-20%] [2], and the present guideline recommend the thrombolytic therapy in patients with intermediary-high risk while

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anticoagulant therapy is indicated in patients with intermediary-low risk PE.

There are a lot of studies evaluating the benefit of thrombolysis in patients with intermediary risk PE compared to anticoagulation therapy. The Pulmonary Embolism Thrombolysis [PEITHO] trial was a multicentre, randomized, double-blind comparison of thrombolysis with a single weight-adapted bolus of tenecteplase plus heparin vs. placebo plus heparin [3]. Patients with acute PE were eligible for the study if they had RV dysfunction, confirmed by echocardiography, and RV pressure overload confirmed by a positive troponin I or -T test. The study included 1006 patients. The primary efficacy outcome, a composite of all-cause death or haemodynamic instability/collapse within 7 days of randomization, was significantly reduced with tenecteplase [2.6% vs. 5.6% in the placebo group; P = 0.015; OR 0.44; 95% CI 0.23–0.88]. The benefit of thrombolysis was mainly achieved by a significant reduction in the rate of haemodynamic instability [1.6% vs. 5.0%; P = 0.002]; there was no statistical difference regarding the all-cause 7-day mortality was low: 1.2% in the tenecteplase group and 1.8% in the placebo group [P = 0.43] [1]. In another randomized study comparing low molecular weight heparin [LMWH] alone vs. LMWH plus an intravenous bolus of tenecteplase in intermediate-risk PE, patients treated with tenecteplase had better functional capacity [3].

Thrombolytic treatment carries a risk of major bleeding, including intracranial haemorrhage. Increasing age and the presence of comorbidities have been associated with a higher risk of bleeding complications [4]. This meta-analysis showed that patients over 70 years old [y.o.] had a statistical significant higher bleeding risk compared to patients under 50 y.o. [OR 3.9]. Meanwhile the bleeding risk increased 4% /year of age. Another groups with high bleeding risk were patients with body mass index [BMI] >30 or BMI <18.5 [OR 2.5]. Chronic diseases [chronic kidney disease, chronic obstructive lung disease] also had higher bleeding risk associated to thrombolytic therapy.

In a recent meta-analysis of Cao et al. [5] which included seven studies involving 594 patients, the cumulative effect of thrombolysis, compared with intravenous heparin, demonstrated no statistically significant difference in mortality [2.7% versus 4.3%; RR=0.64 [0.29-1.40]; P=0.27] or recurrent PE [2% versus 5%; RR=0.44 [0.19-1.05]; P=0.06]. Thrombolytic therapy did not increase major hemorrhage compared with intravenous heparin [4.5% versus 3.3%; RR=1.16 [0.51-2.60]; P=0.73], but it was associated with an increased minor hemorrhage [41% versus 9%; RR=3.91 [1.46-10.48]; P=0.007]. Meanwhile, another meta-analysis of Nakamura et all. [6] which included A total of 1510 patients showed no significant differences in the composite endpoint of all-cause death or recurrent PE between the adjunctive thrombolytic therapy arm and the heparin-alone arm [3.1% vs. 5.4%; RR, 0.64 [0.32-1.28]; P = 0.2]. Adjunctive thrombolytic therapy significantly reduced the incidence of the composite endpoint of all-cause death or clinical instability [3.9% vs. 9.4%; RR, 0.44; P < 0.001]. There were no statistically significant associations for major bleeding when adjunctive thrombolytic therapy was compared with heparin therapy alone [6.6% vs. 1.9%; P = 0.2].

These results underline the importance of defining the major bleeding and minor bleeding criteria. The last International Society of Thrombosis and Haemostasis [ISTH] criteria define major bleeding in non-surgical patients as having a symptomatic presentation and fatal bleeding, and/or bleeding in a critical area or organ [such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome], and/or bleeding causing a fall in hemoglobin level of 20 g L-1 [1.24 mmol L-1] or more, or leading to transfusion of two or more units of whole blood or red cells [7]. The criteria for clinical relevant non-major bleeding include any sign or symptom of hemorrhage [e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone] that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: a) requiring medical intervention by a healthcare professional; b)leading to hospitalization or increased level of care; c)prompting a face to face [i.e., not just a telephone or electronic communication] evaluation [7]. The haemodynamic instability was defined as medium BP <90mmHg or a drop in SBP >50mmHg from baseline [2]. These results underline the need to improve the safety of thrombolytic treatment in patients at increased risk of

intracranial or other life-threatening bleeding or to better assess the groups of patients referred to thrombolytic therapy.

Material and Methods

The study objective is to assess the effects of thrombolytic therapy on clinical markers in patients with acute intermediary – high risk PE [Mt, haemodynamic instability, DP and medium BP] and also to analyse the bleeding risk in the study groups [as bleedings were the major limiting factor in using thrombolytic therapy in intermediary risk PE patients]. As an original feature of the present study we evaluated the post-thrombolytic BP recovery and the effect on DP.

This study was a randomized, prospective one, including 65 patients with intermediary-high risk acute PE [symptom onset in the last 2 weeks], with no history of previous PE. The inclusion criteria were selected in order to assess the effect of thrombolytic therapy without any pitfalls related to pre-existing pulmonary hypertension caused by a previous PE.

The exclusion criteria included three types of factors. First of all, the factors which could have caused a pre-existing pulmonary hypertension which may have affected the assessment of the effect of thrombolysis on patient's haemodynamic status. In this group we included: pre-existing PE, cardiomyopathies with decreased LVEF [LVEF<30%], pre-existing pulmonary hypertension, valvulopathies associated with pulmonary hypertension. In the second category we included the factors associated with high bleeding risk: severe anemic syndromes [Hb<8g/dl], severe anticoagulation disorders [ex: hepatic cirrhosis, haemophilia], age over 80 y.o. In the last category of exclusion criteria were included psychiatric disorders, with impossibility of informed consent and end stage neoplasms.

The patients were divided in two groups, thrombolysed group [study group] - 28 pts – and unthrombolysed group [control group] – 37 pts -. Patients in study group were treated with ateplase [t-PA] 10mg bolus and 90 mg in 2h associated with unfractionated heparin [UFH], while patients in control group received UFH alone, with activated partial thromboplastin time [aPTT] control.

Patients were selected in study group taking into account the results of Mikola meta-analysis which revealed the main factors associated with high bleeding risk in thrombolysed patients. The patients included in study group had a BMI 18.5-29, did not have severe CKD [Creatinine Clearence >30ml/min/m^2] and did not have any contraindication for thrombolysis.

The method consisted in assessing the evolution of continuous and nominal variables during the admission, in relation to the type of treatment the patient received. The continuous variables included assessment of RV overload , of patient's haemodynamic status and the bleeding rates. The variables used to assess the RV overload were: a) N terminal Pro Brain Natriuretic Peptide [Nt pro BNP] on admission and on 7th day [as a marker of RV pressure overload]; b) RV end diastolic diameter and the ratio between the RV end diastolic diameter and LV end diastolic diameter [RVEDD/LVEDD] evaluated by transthoracic echocardiography on admission and on 3rd day as markers of RV pressure overload; c) myocardial contraction velocity [MCV] on the RV wall and tricuspid annulus pick systolic excursion [TAPSE] on admission and on 3rd day as markers of RV systolic function, correlated to RV acute pressure overload.

The continuous variables used to assess the haemodynamic impact of the two therapies were medium SBP , medium blood pressure [MBP] and DP on admission [10 measurements on 30 min in admission] and on 24 h [automatic blood pressure monitoring [ABPM]].

The variables used to evaluate the bleeding risk were the major and minor bleeding rates in the two groups, on admission and on 5th day.

The nominal variables were the sex distribution in the two groups and the early [7th day] Mt and haemodynamic instability rate in the two groups.

For the statistical analyse we used t-test assuming equal variances, analysis of variance [ANOVA] as statistical tests and Epi-Info program.

Results

There were no significant differences between the two groups regarding the sex distribution [males

1:2.33 vs 1:2.47, p 0.07]. There was a significant difference regarding the medium age between the two groups [study group vs control group : 63.32+/- 13.4 vs 68.58 +/- 15.1 [p 0.005]]. This difference can be explained by the selection criteria, as patients with severe CKD and COPD were included in the control group, and age is a factor for increasing incidence of these diseases. No statistical significant difference was noticed between the two groups regarding the PESI score [PESI study vs control: 113.5 +/- 12 vs 113.28 +/- 13 , p 0.53].

The evaluation of the parameters of RV overload revealed a statistical significant better improvement in study group patients compared to control group patients. There was no difference between the RVEDD on inclusion between the two groups [study vs control: 47.1 +/- 3.4 mm vs 43.94 +/- 2.9 mm [p 0.09]] but on 72h was noticed a statistical significant difference regarding the decrease of RVEDD [22.08% study group vs 11.49% control [p 0.03]] (Figure 1).

This fact can be explained by the decrease of the RV pressure overload after the thrombolytic therapy which may lower the RV workload and the RVEDD. Regarding TAPSE in the study group was identified a statistical significant increase on 72 h with 48.27% vs 26.88% in control [p 0.03] (Figure 2).

Regarding haemodynamic instability on 7th day we noticed a significant difference between the two groups, that can be explained by the effect of the thrombolytic therapy on RV overload markers compared to UFH therapy. The haemodynamic instability rate was 1:9.33 in the study group vs 1:3.77 in control group [p 0.03] (Figure 3). There was no significant difference between the two groups regarding early mortality rate.

On the assessment of the effect of thrombolytic therapy on BP profile and DP, there was no difference between the two groups regarding SBP [123.4 +/- 5mmHg vs 125.2 +/- 4.2mmHg], MBP or DP on admission. The frequency of hypertensive patients was higher in the control group [1:2.8 study vs 1:2.17 control [p 0.02]] this difference being explained by the higher medium age in control group.

We identified a statistical significant difference between the medium SBP recovery on 24 h between the two groups [increase 17.99% in study group vs 14.05% in control group [p 0.04]], secondary to the increase of LV stroke volume caused by the increasing preload. Also, the DP had a statistical significant

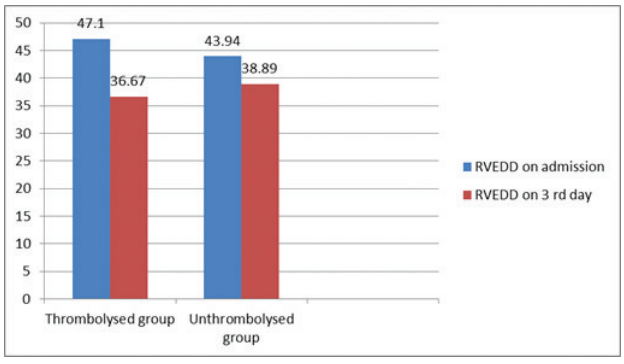

Figure 1: The RVEDD variation in the two groups on the 3rd day compared to admission, showing a more important decrease in the study group compared to control group. [personal processed data]

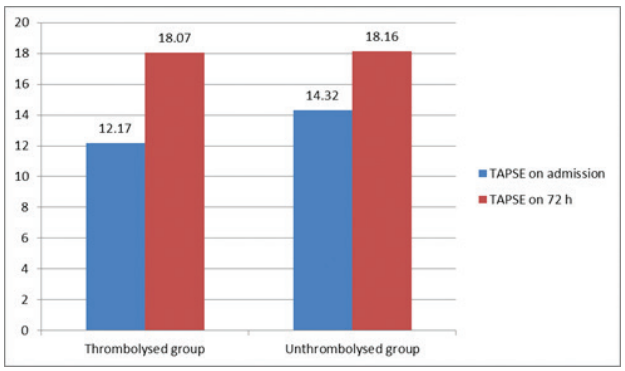

Figure 2: TAPSE variation in the study group and control group on 72 h compared to admission value [personal processed datas]

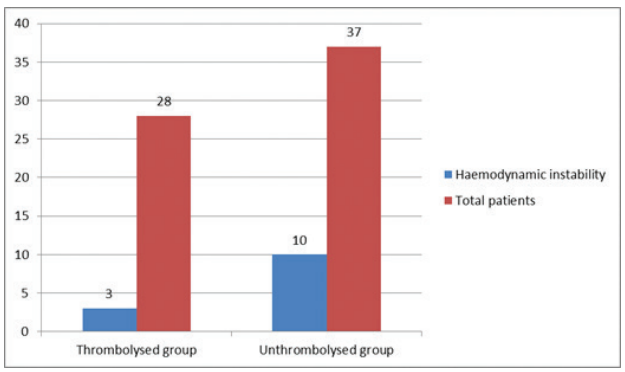

Figure 3: The evolution of the 7th day haemodynamic instability rate in the two groups [personal processed datas]

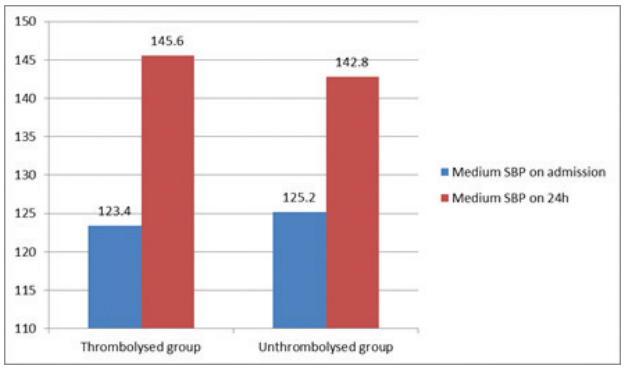

Figure.4: The medium SBP evolution in the study group compared to control group at 24 h compared to admission [personal processed datas]

decrease in the study group compared to inclusion [decrease 11.74% in study group vs 8.6% in control group [p 0.04]]. The impact of heart rate on the DP value and the reduce of tachycardia rate can explain the decrease of DP compared to the increase of medium SBP. Taking into acount the fact that DP is the expresion of LV workload the reduce of LV workload is another positive effect of thrombolytic therapy. (Figure 4)

Discussion

The thrombolytic therapy in intermediary-high risk PE remains a debatable issue, since the bleeding risk is the main factor to limit the use of thrombolytic agents. Nevertheless, the assessment of bleeding risk by identifying the risk factors is a very important point in the acute management of these patients.

In the present study we tried to identify the best patient profile which may benefit most of thrombolytic therapy, without increasing bleeding risk. We also assessed the effect of thrombolysis by using haemodynamic markers [SBP recovery, DP evolution], biochemical and imagistic ones [TAPSE, RVEDD]. The correlation between these markers and the main clinical prognostic makers [haemodynamic instability and mortality] is sustained by the impact of the therapy on these markers. The positive effect on these markers was not associated with an increasing bleeding risk, this fact leading to an increasing safety profile of the studied therapy.

Conclusions

The benefic effect of thrombolytic therapy on RV dysfunction and haemodynamic instability is proved by the statistical significant improvement in the biochemical and imagistic markers of RV dysfunction post-thrombolysis. Meanwhile, the effect on these markers is sustained by a lower instability rate in the thrombolysed group compared to control group.

These effects were associated with a good risk profile, regarding a non-significant statistical difference between the two groups regarding the major or minor bleedings. The negative element of the study is the low cohort and the RV shape presumption [by using TTE], because the 3D-echocardiography could not be used in emergency on admission.

The future research directions regarding this important problem relates to a better assessment of RV systolic function – by using 3D-ecocardiography or myocardial strain for RV – and an improvement of patient database.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

List of abreviations

BP – blood pressure;
PE - Pulmonary embolism;
RV – right ventricle;
y.o. – years old;
LV – Left ventricle;
LVEF – Left ventricle;
SBP – Systolic blood pressure;
DP – double product;
PESI – Pulmonary embolism severity index;
Mt – mortality;
LMWH – low molecular weight heparin;
BMI – body mass index;
COPD – chronic obstructive pulmonary disease;
CKD – chronic kidney disease;

ISTH – International Society of Thrombosis and Haemostasis;
Hb – hemoglobin;
t-PA – ateplase;
UFH – unfractionated heparin;
apTT – activated partial thromboplastin time;
Nt-pro BNP – N terminal Pro Brain Natriuretic Peptide;
TAPSE – tricuspid annulus pick systolic excursion;
RVEDD – right ventricle end-diastolic diameter;
LVEDD – left ventricle end-diastolic diameter;
MCV – myocardial contraction velocity;

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