PULMONER EMBOLİDE TROMBOLİTİK TEDAVİ VE KONVANSİYONEL TEDAVİ ETKİNLİĞİNİN 10. GÜNDE KARŞILAŞTIRILMASI

COMPARISON OF THROMBOLYTIC AND CONVANSIONAL TREATMENT EFFICIENCY IN PULMONARY EMBOLISM ON THE 10TH DAY OF TREATMENT

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Anahtar sözcükler: Pulmoner emboli, pulmoner BT anjiyografi, r-TPA

Keywords: Pulmonary embolism, pulmonary CT angiography, r-TPA

Geliş tarihi: 09 / 06 / 2017 Kabul tarihi: 30 / 10 / 2017

ÖZ

Amaç: *Trombolitik tedavinin hastaya sadece ilk birkaç gün fayda sağladığı, 1. haftadan sonra ise sadece antikoagülan tedavi alanların da benzer trombüs erime oranlarına sahip oldukları düşünülmektedir. Bu çalışmanın amacı trombolitik tedavinin 10. gününde hastaların klinik parametrelerine ve Pulmoner Arter BT Obstrüksiyon İndeksi açılma oranlarına etkisinin olup olmadığının araştırılmasıdır.*

Yöntem ve Gereç: *Çalışmaya pulmoner tromboemboli tanısı konmuş 28 olgu alındı. Trombolitik tedavi verilmesinin uygun görüldüğü 15 hasta çalışma grubuna (grup 1), kalan 13 hasta ise konvansiyonel tedavi(antikoagülan tedavi) grubuna (grup 2) alındı. Tedavinin semptomların başlamasından sonraki ilk 14 günde başlandığı hastalardan trombolitik (r-TPA) verilenler grup 3, verilmeyenler grup 4 olarak planlandı. Çalışma grubundaki hastalara tanı konulduğu anda protokole göre trombolitik tedavi uygulandı ve ardından antikoagülan tedavi ile devam edildi. Kontrol grubundaki hastalara sadece antikoagülan tedavi verildi. Geliş sırasında ve 10. günde pulmoner BT anjiyografi, transtorasik ekokardiyografi, arteryel kan gazı çalışıldı. PABTOİ hesaplandı. Veriler tedaviden önce ve tedaviden sonra 10. günde gruplar arasında karşılaştırıldı.*

ABSTRACT

Aim: *Benefit of thrombolytic therapy for the patients with pulmonary embolism is thought to be in only the first few days and it's considered that after the first week anticoagulation therapy has similar rates of resolution. The purpose of the study is to investigate the effect of thrombolytic therapy on the patient's clinical parameters and Pulmonary Artery CT Obstruction Index opening rates on the tenth day.*

Material and Methods: *In this study, 28 pulmonary embolism cases were investigated. Taken in to consideration clinical, radiographic, echocardiographic, biochemical findings, and contraindications to thrombolytic therapy, 15 patients enrolled to the thrombolytic therapy group (group 1) and the remaining 13 patients were included in the conventional therapy (group 2).Patients given thrombolytic therapy(r-TPA) in the first 14 days after pulmonary embolism was planned as group 3 and treated with anticoagulants only as group 4. Pulmonary CT angiography, transthoracic echocardiography (ECHO), arterial blood gasses were studied on admission and tenth day. PACTOI was calculated from pulmonary CT angiography.*

Bulgular: *Gruplar arasında başlangıç kriterlerinde istatistiksel olarak anlamlı farklılık saptanmadı. Grup 1'de 10. günde %52.8±25.5'lük açılma oranı elde edilirken, grup 2'de bu oran %42.5±20.0 olarak saptandı. Grup 3'de10. günde açılma oranı %58.4±24.5'e ulaşırken, grup 4'de bu oran %42.2±22.2 bulundu. Tedavinin 10. gününde grup 3'deki hastalarda grup 4'e göre PO2, SaO2 ve PAB değerlerinde anlamlı düzelme bulundu (p<0.05).*

Sonuç: *Sonuç olarak, pulmoner embolinin akut döneminde yararı bilinen trombolitik tedavinin, yalnız konvansiyonel antikoagülan verilen gruba göre daha iyi BT açılma oranları, AKG ve EKO bulgularının olması tedavinin 10. gününde bile yararlı olduğunu göstermiştir.*

Results: *Differences were insignificant between the groups for the initial criteria. Opening rate on the tenth day was 52.8%±25.5 in group 1 and 42.5%±20.0 in group 2. In patients of group 3 opening rate was 58.4%±24.5 on the tenth day, whereas in group 4 it was 42.2%±22.2. Significant improvements on PO2, SaO2 and PAP was seen in group 3 patients at the tenth day when compared with group 4 (p<0.05).*

Conclusion: *As a conclusion it is shown that patients receiving thrombolytic therapy had better PACTOI and ABG and ECHO findings at the tenth day.*

INTRODUCTION

Pulmonary embolism (PE) is a disease with increasing frequency due to the evolving diagnostic methods, with a wide clinical spectrum from asymptomatic cases up to sudden death and with high overall mortality and morbidity rates. PE incidence is determined as 12-64 % in autopsy series and has been thought to be responsible for 5.4% of all hospital mortalities (1,2). The main treatment of disease is anticoagulation. Higher mortality rates of massive and sub-massive diseases mark the necessity of other agents in treatment (3,4). In guidelines, anticoagulation with thrombolytic treatment is recommended in massive embolism, and in only some selected cases thrombolytic treatment is recommended for sub-massive disease (3,4,5). As of indicated, it may not be correct to wait hypotension in these patients each time (6). Sometimes to wait may also threat patient's life. May be it should be given up to limit the high-risk concept with hypotension in guidelines and radiologically diagnosed massive pulmonary embolism patients with the low oxygen pressure, high PAP (pulmonary artery pressure) and signs of right ventricle dilatation should be included in the high risk group. Benefits of thrombolytic treatment have been shown. But, it is thought that, there is no considerable difference between thrombolytic and conventional treatments after the first week. The basis of this idea depends on the studies performed with ventilation/perfusion (V/Q) scintigraphy investigating the effects of thrombolytic treatment (7-10). However, nowadays, V/Q scintigraphy left it's place to computed tomography (CT) angiography. Especially computed tomography pulmonary angiography is more sensitive in PE diagnosis and may directly show thrombus (11-12).

Randomized controlled trials with very high number of patients are necessary since generally there are many accompanying risk factors present in these patients. The amount of occlusion of vascular bed after first week in the patients having anticoagulation or thrombolytic therapies is still continues to be controversial.

In this study, the differences in resolution of embolism are investigated in submassive pulmonary thromboembolism, among patients treated with or without thrombolytic regimens, on the 10th day of treatment with the findings of ABG (arterial blood gases), ECHO (echocardiography) and pulmonary CT angiography.

MATERIAL AND METHODS

This study is a prospective, case-controlled clinical trial. Local Ethics Board permission has been obtained for the study. Ethics Board localization, permission number and date was reserved and hidden for blinding.

Twenty eight patients with PE, diagnosed by pulmonary CT angiography, laboratory and clinical findings were included in the study. Trans-thoracic echocardiographies (ECHO) were performed for all patients and the findings of right ventricular enlargement and/or hypokinesis of the free wall, leftward septal shift, and evidence of pulmonary hypertension were recorded. If right ventricular dysfunction is seen on cardiac ultrasonography, the diagnosis of acute submassive, pulmonary embolism is supported. Written informed consent has been obtained from all patients who agreed to participate in the study.

Demographic characteristics of patients, application dates, time passed from the onset of symptoms till the initiation of the treatment, laboratory results, ABG values, PACTOI values, lower extremity venous compression ultrasound (CUS) and transthoracic ECHO findings were recorded to the detailed patient form. On the 10^{th} day, ABG, transthoracic ECHO and pulmonary CT angiography results of these patients were also recorded. Those patients who are younger than 18 years of age or pregnant or who have renal failure or another contraindication for CT evaluations were excluded from the study. Fifteen patients that were evaluated to be suitable for thrombolytic treatment (according to clinical, radiological and laboratory values) were included in the thrombolytic treatment group (group 1). Thirteen patients were evaluated to be not suitable for thrombolytic treatment (according to clinical, radiological and laboratory values) conventional anticoagulant treatment regimen was given in the conventional treatment group (group 2). One patient with older age, two patients with peptic ulcer, one patient with the history of intracranial hemorrhage, two patients who refused the thrombolytic treatment and seven patients who were clinically stable were incorporated to the conventional treatment group (group 2). Three patients in group 1 received thrombolytic therapy after 14 days of the disease because of late admission to hospital.

Patients who received the thrombolytic treatment in first 14 days of symptoms were sub-grouped as group 3 (n=12) while patients who received only conventional treatment in first 14 days were sub-grouped as group 4 (n=10) and these 2 groups were also compared with each other. All patients were diagnosed with moderate-severe risky group pulmonary embolism according to the 2014 classification of the European Society of Cardiology (ESC) (4). To the patients in thrombolytic treatment group, just after the diagnosis was established, 100 mg r-tPA was given by the peripheral intravenous way in 2 hours. During treatment, patients were monitorized. At the end of this treatment, enoxaparin sodium at the adjusted dosages with the patients weight, was started. Warfarin was administered to patients again after at least 5 days of enoxaparin sodium treatment till INR value reach to 2.0-3.0 range. Enoxaparin sodium was discontinued and the treatment was only carried on with warfarin.

On the other hand patients in control group received only enoxaparin sodium. Again warfarine was given after at least 5 days of LMWH (enoxaparin sodium) treatment and when INR value reached the 2-3 range, enoxaparin sodium was discontinued and the treatment was only carried on with warfarin.

Pulmonary CT angiography was performed to all patients in admission and on the 10th day of treatment. Lower extremity venous doppler was applied to all patients in admission. The admission and 10^{th} day CT, ABG and ECHO findings of patients were compared as group 1 with 2 while group 3 with 4. Multi-slice CT (Aquillion 64, Toshiba, Tokyo, Japan) has been used for CT estimations. CT images were evaluated by an experienced radiology specialist on thorax radiology and two chest diseases specialist. Radiologist was blind about the clinical, laboratory and other radiological findings of cases. Pulmonary artery obstruction index was calculated by radiology specialist according to the formula developed by Qanadli et al. (13) and proven in many studies.

The percentage of obstruction was calculated by dividing the patient score by the maximal total score and by multiplying the result by 100. The pulmonary artery CT obstruction index can be expressed as: $(n \cdot d)/40 \times 100$, where n is the value of the proximal thrombus in the pulmonary arterial tree equal to the number of segmental branches arising distally (minimum:1; maximum:20) and d is the degree of obstruction (minimum:0; maximum: 2) (13).

Embolus absorption ratio on the 10^{th} day control has been obtained with the formula shown below:

PACTOI Percentage Change= ((1^{st} day PACTOI -10^{th} day PACTOI) /1^{st} day PACTOI) x100

Bilateral lower extremity compression ultrasounds were performed with Toshiba Powervision 6000 (Japan) brand device and the results were recorded. ECHO was performed with Vivid 7 pro brand device and the results were documented.

The improvements in ABG and ECHO on the 10^{th} day were expressed as percentage changes according to the admission. Results were calculated using the following formulas.

pCO_2 % change = ((10^{th} day pCO_2 - 1^{st} day pCO_2) /1^{st} day pCO_2) x 100

pO_2 % change= ((10^{th} day pO_2 – 1^{st} day pO_2) /1^{st} day pO_2) x100

SaO_2 % change = ((10^{th} day SaO_2 -1^{st} day SaO_2) / 1^{st} day SaO_2) x100

PAP % change = ((1^{st} day sPAP -10^{th} day sPAP) /1^{st} day PAP) x100

Statistical analysis

SPSS 16.0 program was used for data analysis. Frequencies (%) were used for categorical variables and mean±standard deviations or medians (min.-max.) was used for continuous variables. Chi-square test was used for comparison of categorical variables; Student t-test (independent samples t-test) and Mann-Whitney U-test were used for comparison of independent continuous variables of the study groups. Spearman correlation coefficient was calculated for biomarkers that yielded statistical significant differences between groups. $p<0.05$ was set for the statistical significance threshold.

RESULTS

Totally 28 patients diagnosed with submassive embolism, with the ages ranging from 29 to 83; 15 who had thrombolytic treatment and 13 who had conventional treatment were investigated. In regards to demographic features and initial PACTOI, PAP and ABG, there were no significant differences between groups. The comparisons of properties of cases are summarized in Tables 1 and 2.

The comparisons of percentile changes in PACTOI, pCO_2, pO_2, SaO_2 and PAP values on the 10^{th} day of treatment, among all patients and among patients treated in first 14 days are shown in Table 3 and 4.

Table 1. Comparison of characteristics of cases

	Group 1 (n=15)		**Group 2 (n=13)**		
Characteristics	**Mean±SD**	**Median(Range)**	**Mean±SD**	**Median(Range)**	**P value**
Male/Female	6/9		4/9		>0.05
Age, years	59.9±17.5	64 (29-83)	58.8±15.9	65 (25-76)	>0.05
Admission time, day	7.2±8.7	3 (1-30)	8.0±8.1	5 (1-30)	>0.05
Treatment onset time ,day	8.4±8.8	5 (1-30)	8.0±8.1	5 (1-30)	>0.05
Admission PACTOI, %	57.3±7.3	57.5 (42.5 -72.5)	52.0±10.0	50 (37.5 -72.5)	>0.05
Admission PAP, mm Hg	57.1±11.5	55 (40-85)	48.5±11.3	45 (30-70)	>0.05
Admission pO_2, mm Hg	52.6±9.7	52 (37 -71.2)	56.4 ±12.9	55.8 (34.9-79)	>0.05
Admission SaO_2, %	86.0±8.2	89.2 (63 -95.2)	87.8±9.2	91 (60.1 -95.2)	>0.05
Admission pCO_2, mm Hg	28.6±4.6	29.6 (19 -38.2)	32.6±6.3	30.5 (27.3 -52.1)	>0.05

Group 3: *Patients receiving the thrombolytic treatment in first 14 days.*
Group 4: *Patients receiving the conventional treatment in first 14 days.*

Table 2. Comparison of characteristics of cases treated in first 14 days

	Group 3 (n=12)		**Group 4 (n=10)**		
Characteristics	**Mean±SD**	**Median (Range)**	**Mean±SD**	**Median (Range)**	***P* value**
Male/Female	3/ 9		3/7		>0.05
Age, years	58.0±19.2	58.5 (29-83)	55.5±16.7	60.5 (25-76)	>0.05
Admission time, day	3.3±2.7	2 (1-10)	4.5±3.1	3.5 (1-10)	>0.05
Treatment onset time, day	4.5±3.7	4 (1-12)	4.5±3.1	3.5 (1-10)	>0.05
Admission PACTOI, %	57.2±8.2	58.8 (42.5 -72.5)	50.1±10.4	46.3 (37.5 -72.5)	>0.05
Admission PAP, mm Hg	55.1±7.4	54.5 (40-68)	49.0±12.6	45 (30-70)	>0.05
Admission pO_2, mm Hg	50.4±9.2	49.3 (37 -71.2)	57.1±13.9	57 (34.9-79)	>0.05
Admission SaO_2, %	84.5±8.5	85.9 (63 -95.2)	87.6±10.4	91.1 (60.1 -95.2)	>0.05
Admission pCO_2, mm Hg	27.7 ±4.1	29.4 (19 -32.8)	32.5 ±7.2	30.2 (27.3 -52.1)	>0.05

Group 3: *Patients receiving the thrombolytic treatment in first 14 days.*

Group 4: *Patients receiving the conventional treatment in first 14 days.*

Table 3. The evaluation of percentile changes in PACTOI, ABG, and PAP on the 10th day of treatment according to the type of treatment among all cases**.**

	Group 1 (n= 15).		**Group 2 (n= 13)**		
Change (%)	**Mean ±SD**	**Median (Range)**	**Mean ±SD**	**Median (Range)**	***P* value**
PACTOI, % change	±25.5 52.8	50 (13.6-100)	42.5±20.0	40.9 (15.8-80)	>0.05
pCO_2, % change	22.6±18.3	22 (-5.76 -62.56)	10.0±13.2	8 (-28.6 -11.37)	**<0.05**
pO2, % change	38.2±20.4	37 (2.7 -84.3)	26.3±22.4	12.9 (3.4 -61.1)	>0.05
SaO_2, % change	10.7±10.6	7.3 (0.4 -42.5)	7.5±10.4	3.2 (0.4 -39.8)	>0.05
PAP, % change	41.7±15.6	41.7 (12.5 -70.6)	26.9±15.1	(0 -53.9) 28.6	**<0.05**

Group 3: *Patients receiving the thrombolytic treatment in first 14 days.*

Group 4: *Patients receiving the conventional treatment in first 14 days.*

Table 4. The evaluation of percentile changes in PACTOI, ABG, and PAP on the 10th day of treatment according to the type of treatment among cases treated in first 14 days.

	Group 3 (n=12)		**Group 4 (n=10)**		
Changes in %	**Mean±SD**	**Median Range)**	**Mean±SD**	**Median (Range)**	***P* value**
PACTOI, % change	58.4±24.5	54.2 (20-100)	42.2±22.2	40.7 (15.8-80)	>0.05
PACTOI, % change	25.5±18.5	22.8 (6 -62.6)	10.7±14.4	10.2 (-11.4 -28.6)	>0.05
pCO_2, % change	44.1±17.5	41 (23.3 -84.3)	26.1±21.8	14.2 (3.4 -56.5)	**<0.05**
pO_2, % change	12.7±10.9	11.3 (1.7 -42.5)	7.9±11.7	3.2 (0.4 -39.8)	**<0.05**
SaO_2, % change	40.4±11.5	40.8 (20 -59.7)	27.5±17.2	31 (0 -53.9)	**<0.05**

Group 3: *Patients receiving the thrombolytic treatment in first 14 days.*

Group 4: *Patients receiving the conventional treatment in first 14 days.*

Both from each group, treatment started 14 days after the onset of symptoms, on 3 patients.

Among all patients and among patients treated in first 14 days, it was reported that, PACTOI percentile changes were higher in patients receiving thrombolytic treatment. The mean, standard deviation, minimum and maximum values PACTOI percentile changes in all patients treated with thrombolytic treatment and conventional treatment are shown in Fig.1.

There was no statistically significant correlation between the PACTOI percentage changes on the 10th day of treatment and the onset day of treatment. However, it was found that with the delay in onset of the treatment, in both thrombolytic and conventional treatment groups, PACTOI percentage changes on the 10th day were decreased. This relationship is shown in Figure 2. It is remarkable that, there were 2 patients in thrombolytic treatment group in whom PE were 100% improved which shown in Figs. 3 (a and b).

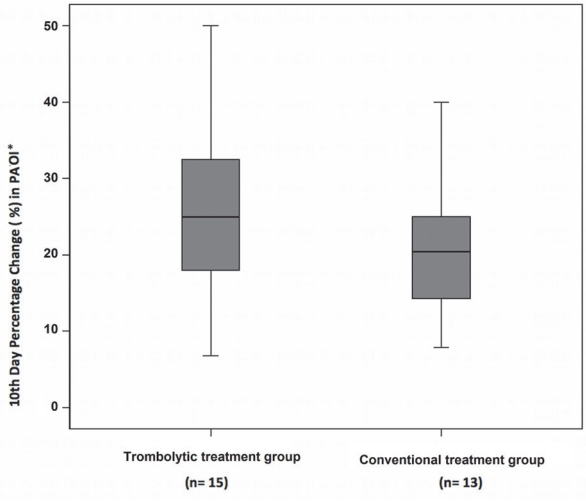

Figure 1. PACTOI percentage changes on the 10th day, according to the shape of treatment.

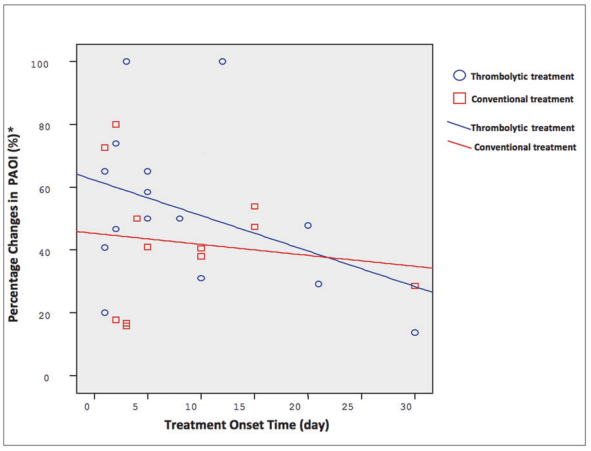

Figure 2. The relationship between percentage changes in PACTOI on 10th day and onset time of treatment.

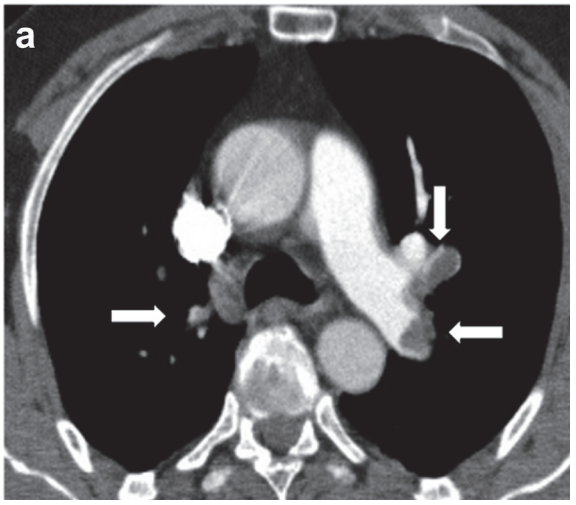

Figure 3. **a.** CT pulmonary angiography of the patient before thrombolytic treatment.

DISCUSSION

Pulmonary thromboembolism is a disease with increasing importance in recent years, with difficulties in diagnosis, and question marks in treatment causing acute and chronic problems. Due to its large clinical spectrum ranging from asymptomatic disease to sudden death, it is evident that every patient cannot

be treated similarly. In management of these patients, not only quick resolution of embolism to overcome the acute problems but also full resolution of embolism to prevent CTEPH development in chronic period should be aimed.

In literature, it has been thought that after the acute effect of thrombolytic treatment, approximately in first week, thrombolytic non-receiving patients also have the similar thrombus absorption rates (7-10). The basis of this idea depends on previous reports like PAIMS-2, determined similar embolism absorption rates in both groups in first week. In PAIMS-2 study, patients receiving thrombolytic and conventional treatments were compared with pulmonary angiography in 24th hour, and V/Q scintigraphy at the end of 1st week and 1st month. In this study it has been reported that, in 24th hour the thrombolytic receiving group was having better emboli absorption rates however this difference was not present after the first week (10).

Nevertheless, it is evident that, it is not possible to predict the emboli absorption rates with V/Q scintigraphy in subacute periods of PE due to parenchymal alterations and vascular changes like hypoxic vasoconstriction (14-16). Owing to these changes, the usage of V/Q scintigraphy in not only prediction of emboli absorption rates but also in diagnosis of PE after the 24th hours is controversial (17). Moreover, in a study it has been determined that, lung perfusion defects determined in V/Q scintigraphy do not show the intravascular clot correctly (18). It has been determined in many studies that, CT angiographies, especially new generation ones, may correctly determine emboli burden and correlate with the clinic (19-23). In our study, in all patients receiving thrombolytic treatment (n=15), on the 10th day of treatment, an absorption rate of 52.8±25.5% was determined in PACTOI with pulmonary CT while this ratio was 42.5±20.0% in conventional treatment group (n=13).

When patients started to be treated in first 14 days after the onset of symptoms are regarded, in patients receiving thrombolytic treatment (n=12), on the 10th day of treatment, an absorption rate of 58.4±24.5% was determined in PACTOI while this ratio was 42.2±22.20% in conventional treatment group (n=10). The low number of patients may be the reason that both of the differences were not statistically significant. Moreover, though there was 100% healing in 2 patients in thrombolytic treatment group, the best improvement ratio was only 80% in other group. In 3 patients received thrombolytic treatment after fourteenth day, the PACTOI was improved with a ratio of 29.0±17.3% in average on 10th day. When the improvement ratio of 43.6±13.0 % in PACTOI in average in 3 patients received conventional treatment after fourteenth day is regarded, it has been determined that thrombolytic administration after fourteenth day does not have any prominent effects in emboli absorption. When patients were evaluated together whether they received thrombolytic or not, in patients who were started to be treated in first 14 days (n=22) the absorption rate of 51.0±24.3% was determined in PACTOI while this ratio was 36.3±15.9% in patients who were started to be treated after 14 days (n=6). The statistically insignificance of this difference was also thought to be due to the low number of patients.

Additional to absorption rate, patients were evaluated in regards to ABG and ECHO findings. When all patients were evaluated, in thrombolytic treatment group better improvement ratios were recorded in pCO_2, pO_2, SaO_2 and PAP values than conventional treatment group, in 10th day. The statistically significant increase in pCO_2 showing the decline in hyperventilation in thrombolytic group was thought to be due to better improvement in PACTOI.

In patients with acute PE, the condition of right ventricle has a critical importance in

determination of prognosis of patient and effects the thrombolytic treatment decision in patients with submassive pulmonary embolism (5,24,25). The PAP value reflecting the workload of right ventricle, 41.7±15.6% decrease was reported in thrombolytic group on the 10th day control while this ratio was 26.9±15.1% in other group. This difference was statistically significant. This finding suggested that; thrombolytic treatment may provide additional benefits in patients who are stable initially but may have poor prognosis by progressing right ventricle failure in later hours. In comparison of groups received thrombolytic treatments in first 14 days with conventional treatment group, a statistically significant increase in pO_2, SaO_2 values and a statistically significant decrease in PAP values were determined. Our results are in contrast with the results of Konstantinides et al (9) who have reported that, thrombolytic treatment benefits to right ventricle functions only in first days of treatment, and didn't find any difference between the groups after the first week. This may be due to the patients population in their study. The patients having symptoms up to 2 months were included in the study. Moreover, when our results are evaluated, in concordance with the literature, when the thrombolytic treatment has been started earlier, the higher success rate has been determined. In our study, only 3 patients received thrombolytic treatment after the 14th day and the results of these patients were not as successful as the patients received thrombolytic treatment before the 14th day. When statistically significant improvements seen in all 3 parameters we concluded that receiving thrombolytic treatment in first 14 days is better than receiving it later.

Reports in literature about the high bleeding ratios of thrombolytic treatment may result in that clinicians regard the thrombolytic treatment as the last chance in many times (26-27). In patients treated in our clinic no complications due to thrombolytic treatment was observed that may negatively affect the prognosis of patient. Similar with our results, Konstantinides et al (7) did not determine any increased hemorrhagic complications due to alteplase in 118 patients with submassive embolism. The short achievement time results in that, though the most frightened complication, the hemorrhage develops, after the cessation of admission, its affect passes away in minutes and the hemorrhage improves spontaneously without the necessity of any other interventions (28). The important points are that, patients with the high bleeding risk should be determined correctly, the patient should be prepared appropriately before the thrombolytic treatment, and the patient should be observed carefully during admission. We thought that absence of any patients with the unfavorable complications due to thrombolytic treatment in contrast to the literature was due to the election and treatment of patients with meticulousness.

Limitations of our study were; having less number of patients to decide for precisely judgements and we couldn't follow up them for a long time to evaluate chronic pulmonary hypertension. In addition, it was not ethically possible to increase the control group, ie patients in the non-thrombolytic group. Because thrombolytic therapy was needed, but not given due to contraindications.

As a conclusion, improvements of clinical parameters and emboli absorption rates after thrombolytic treatment were found better than conventional therapy on the 10th day. Early administration of thrombolytic treatment may have more benefit in cases with high emboli burden or in cases with right ventricle dysfunction. In those kinds of patients, 'wait and see policy' may result in irreversible and unfavorable results in many times.

ACKNOWLEDGEMENTS

We thank Aydın Kurt M.D. (Radiologist) for assistance with computed tomography interpretations and PACTOI calculations.

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