Association of Chronic Thromboembolic Pulmonary Hypertension with Hereditary and Acquired Risk Factors for Thromboembolism

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Abstract- Thrombophilia increases the incidence of pulmonary thrombosis significantly. Various hereditary and acquired factors are known for thromboembolism. The hereditary factors are two common genetic autosomal mutations including factor V leidan mutation and prothrombin gene mutation. A descriptive-analytical design was conducted on 60 patients with thromboembolism who met the inclusion criteria. Two groups with hereditary and acquired risk factors for thromboembolism (group A, B, each 30 people) were evaluated. All the patients of two groups were evaluated in terms of emboli associated with hereditary and acquired risk factors. Association of thromboembolism risk factors' with pulmonary hypertension were studied at the beginning of the study and six months after the treatment then the results of two groups were compared. Among participants, 31 (56.4%) were men. The mean age of the patients was 44.4±14 years, ranging between 23-75 years. Significant association was observed between the stability of the blood clot in pulmonary vessel, six months after the treatment with genetic risk factors (P=0.03). However, no significant association was between pulmonary hypertension and hereditary and acquired risk factors (P=0.24). Based on the significant association between the hereditary risk factors and pulmonary emboli, by taking special prevention and therapy measurements (e.g. genetic engineering), some pulmonary and mortality complications can be prevented and the patient himself and health care system would benefit from this issue.
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Introduction

Hereditary and acquired factors have an important role in venous thromboembolism. Thrombophilia increases the incidence of pulmonary thrombosis considerably. The hereditary factors are two common genetic autosomal mutations including factor V leidan mutation and prothrombin gene mutation (1).

The most specific test to prove the absolute diagnosis of pulmonary thromboembolism is the selected pulmonary angiography detecting emboli with the size 1-2 mm. Today, CT scan of the chest is diagnosed with contrast agent as an alternative to pulmonary angiography. Today, when new CT scanning with contrast agents is available, angiography is applied when therapeutic interventions including catheter embolectomy or thrombolysis with catheter is required (2).

In various studies, the specificity and sensitivity of CT angiography of pulmonary vessels applied to detect pulmonary thromboembolism are 93%, 98%, respectively and its value is equal to pulmonary angiography (gold standard method for diagnosis of pulmonary thromboembolism). CT angiography of pulmonary vessels is less invasive, rapider and less complicated compared to angiography, and it is performed in respiratory pause of the patient (3). The pulmonary CT angiography is applied to detect the main pulmonary embolism, the change in the size of lobar and segmental, determining the severity, the percent of pulmonary emboli, right ventricular and vestibule hypertrophy (4,5). Pulmonary CT angiography does not present information about hemodynamic and pulmonary hypertension (6). The data for the size and the value of blood clot resolution in pulmonary embolus is contradictory. Fragmentation, fibrinolysis of the clot by the body physiology and recanalization are common

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mechanisms of clot removal. The latter two cases start some weeks after the clot is formed, and they do not have any role in the acute phase (6).

A study conducted by Salah D.Qanadli *et al.,* (2000) on 54 patients (35 men and 19 women; mean age, 56 years) indicated the percentage of vascular obstruction in patients with pulmonary embolism in CT angiography as following. Each right and left pulmonary arteries were regarded to have 10 segments (three to the upper lobes, two to the middle lobes, and five to the lower lobes). The presence of embolus in a segmental artery was scored one point, and embolus in the most proximal arterial level were scored a value equal to the number of segmental arteries. To determine the degree of vascular obstruction, this factor was equal to 1, when partially occlusive thrombus was observed, or 2, with total occlusion or the lack of perfusion.

Isolated subsegmental embolus was considered as a partially occluded segmental artery and was assigned a value of 1. Thus, the maximal CT obstruction index was 40 per patient. The percentage of pulmonary vascular obstruction was calculated as following (7): The calculated score per patient= the degree of obstruction× the number of segmental branches with embolous.

The percentage of pulmonary vascular obstruction= (The score calculated for each patient/40) ×100

The percentage of pulmonary vascular obstruction calculated by this method was compared with the percentage of pulmonary vascular obstruction on pulmonary angiography (as gold standard test), and there was a significant association between them (7).

A few studies have been conducted on this issue all over the world and such study has not been conducted in our region, the present study was aimed to evaluate embolus condition associated with the hereditary and acquired risk factors and its association with pulmonary hypertension, six months after the treatment.

Materials and Methods

A descriptive- analytical design was conducted on 60 patients with thromboembolism who met the inclusion criteria. Two groups with hereditary and acquired risk factors for thromboembolism (group A, B, each 30 people) were evaluated. The total duration of the study was eight months; the data was collected and analyzed from the beginning of November 2010 to July 2011.

Each participant selected by multi-slice CT scan 64 (Siemence Somatom Sensation 64)) of contrast media (Schering BG) Ultavis 370mg, underwent pulmonary CT angiography. The contrast medium was non-ionic soluble in water with 370mg iodine/mm with the contrast medium 60-70cc. Test-bolus or Bolus Trachiking methods were applied based on the patient condition for the interval of contrast injection beginning and scan. The scan was performed in the supine position from the base of the neck to under diaphragm. The slices thickness was 0.6mm. After the scanning, the information was recovered in workstation with the thickness 1mm with slice distance 0.5mm, and it was evaluated by MPR, MIP method. VRT method conducted three-dimensional recovery and absolute diagnosis of acute pulmonary thromboembolism were performed. Two diagnosis processes were used six months after the treatment for each of the patients. All the patients of two groups were evaluated in terms of embolism associated with hereditary and acquired risk factors and its relation with pulmonary hypertension after six months treatment then the results of two groups were compared.

Exclusion criteria

. Heart diseases like valvular heart diseases leading to pulmonary hypertension.
. Congestive heart failure and congenital heart diseases
. Pulmonary disease including obstructive pulmonary disease including Asthma and Chronic obstructive pulmonary disease (COPD).
. Interstitial lung diseases
. Intrapulmonary shunts
. Smoking

Study analysis

The results were analyzed by SPSS (version16) and expressed as mean ± SD, frequency, and percent.. To compare the quantitative variables and qualitative variables, student *t*-test and Qui-square were used, respectively. Paired T-test was also applied. The results were considered significant at $P<0.05$ level.

Results

Five patients of group A were excluded because of the limited access to them and no follow up to undergo CT angiography six months later. The information on 25 patients of the intervention group was analyzed and compared with the control group.

Age and gender description

Totally, 31 patients (56.4%) were men and 24 patients (43.6%) were women, and they were divided

into group A, 18 men (72%). In group B, there were 17 women (56.7%). The mean age of participants was 44.4 ± 14 years, ranging between 23-75 years. The mean age of the group A was 42.9 ± 14.2 years (23-66) and group B 45.6 ± 14 years (28-75).

The description of family history pulmonary thromboendarterectomy (PTE)

Among the studied patients in group A, family history of PTE, was positive for three patients (12%), and it was negative among 22 patients (88%). In group B, family history of PTE was positive for 4 patients (13.3%), and it was negative for 26 patients (86.7%). The difference between two groups was not significant in this regard (P=0.60), and two groups were similar in this variable with no bias about the results.

The description of PTE acquired risk factors among the patients

The description of acquired risk factors of pulmonary thromboembolism among group B patients based on the prevalence is shown in Table 1-1

Table 1. The comparison of risk frequency of acquired factors

Etiology	The group with acquired risk factor (Number-30)
Surgery	12 patients (40%)
Serious trauma	8 patients (26.6%)
Long-term inactivity	4 patients (13.4%)
Cancer	3 patients (10%)
Obesity	3 patients (10%)

The description and comparison of PTE at the beginning of the study

PTE was evaluated once at the beginning of the study and then at the end of six months of treatment for pulmonary embolus in accordance with the formula as following:

The PTE among the patients with hereditary risk factors (group A) was 34.2 ± 26.5 %, ranging 1.5-85 %. It was 33.6 ± 25.4%, ranging between 3-85 % to the patients with acquired risk factors (group B). No significant difference was observed between two groups in terms of pulmonary thromboendarterectomy at the beginning of the study (P=0.93).

The description and the comparison of Residual PTE among two groups

Six months after the treatment, the initial diagnosis process was performed for all the patients of two groups. Four patients (16%) of the group A (those with hereditary risk factors) had PTE. However, no one in group B (those with acquired risk factors) had PTE. In negative participants, the clot was eliminated completely during fibrinolysis and in CT angiography, there was no pulmonary embolus. No significant difference was observed between two groups in terms of residual PTE, six months after the treatment (P=0.03). In other words, the stability relation of blood clots was improved by hereditary risk factors six months after the treatment.

The description and comparison of the pulmonary hypertension (PHTN) among two groups

Six months after the treatment, PHTN of two groups was compared. As it is shown, PHTN was considered pulmonary artery pressure above 20mm Hg. , PHTN was observed among 7 patients (28%) of group A and 5 patients (16.7%) of group B. No significant difference was found between the two groups in terms of PHTN six months after the treatment (P=0.24). The number of the dialysis sessions among patients of group A was 2.7±0.4 sessions (2-3) and 2.8±0.4 sessions among patients of group B (2-3). There was no significant difference between two groups in terms of the number of dialysis sessions per week (P=0.72).

Discussion

The most specific test, to confirm the absolute diagnosis of pulmonary thromboembolism, is the selected pulmonary angiography detecting emboli with the size 1-2 mm. Today, CT scan of the chest with contrast agent is used as an alternative to pulmonary angiography. Today, when new CT scanning with contrast agent is possible, angiography is applied when therapeutic interventions including catheter emboloctomy or thrombolysis with catheter is required (2).

Qanadli *et al.,* (2001) evaluated specific indices to determine the pulmonary occlusion among the patients with pulmonary thromboembolism. The results of the study showed that pulmonary obstruction in PTE was closely associated with emboli in pulmonary branches (7).

The study was conducted on 158 patients with PTE. At first, PTE in group with hereditary risk factors was 43% ± 25% and in the other group was 36.6% ± 10.4% and there was no significant difference (P=0.0001)(7).

Despite the study conducted by Qanadli, PTE of the patients with hereditary risk factors (group A) was 34.2% ± 26.5%, ranging from 1.5-85%. In those with acquired risk factors (group B), PTE was 33.6% ± 25.4%, ranging from 3-85%. The difference between two groups in terms of PTE was not significant at the

beginning of the study (*P*=0.93).

In the study conducted by Qanadli *et al.*, PHTN was observed only in 25 patients (15.8%), and there was not significant association between emboli and the initial PTE (*P*=0.08) (7).

Consistent with the study conducted by Qanadli, PHTN was observed among a group A patients, seven patients and group B patients, five patients. There was no significant difference between two groups in terms of PHTN six months after the treatment.

In another similar study conducted by Lang *et al.*, (2006) in Austria, the hereditary risk factors for pulmonary thromboembolism or gene mutations of PTE were evaluated (8). The most common gene mutations of PTE were factor V leiden and factor II mutation. Among 100 patients, 14 patients (14%) had positive family history of pulmonary thromboembolism (8).

Like the study conducted by Lang et al., the present study showed that among the patients with group A, PTE family history was positive in 3 patients and negative among 22 patients. In group B, PTE family history was positive for 4 patients and was negative among 26 patients. There was no significant difference in this regard in the present study. The present study evaluated gene mutations of pulmonary thromboembolism (e.g. 13 gene mutations) for the first time in Iran.

The genes were divided into terms of gene expression, and zero indicated the negative gene, 1 showed heterozigot gene and 2 indicated homozigot gene. The studied patients were evaluated in terms of the expression of different kinds of genes. The studies have reported that a patient was negative in some genes (the lack of gene expression); some genes were heterozigot, and some genes were homozigot. Consistent with the study conducted by Lang *et al.*, the present study showed the highest frequency of gene mutations for factor V genes, methyl hydrofolate reductase (MTHFR 1298 A/C), ACE gene mutation and the mutation of Tissue plasminogen activator (tPA intron 8D/I).

In a descriptive-analytical study conducted by Andrew *et al.*, it was indicated that the PTE measured by CT angiography was considered as an important predicator of pulmonary embolism (9). The study was conducted on 59 patients with pulmonary thromboembolism. The initial PTE was 22±23.2 %, ranging 3-80%. The ratio of female to male patients was 2 to 1 and age range of the patients was 61±18.4 years.

In the study conducted by Andrew *et al.*, six months after the treatment of diagnosis process , the patients underwent CT angiography and emboli was not removed

completely in two patients and PTE was observed among the patients. There was a significant association between emboli and initial PTE (9).

Along with the study conducted by Andrew, six months after the treatment, the initial diagnosis process was performed for all patients of two groups, PTE was observed among four patients of the of group A (those with hereditary risk factors). However, there was no PTE in group B patients (those with acquired risk factors). In negative participants, the clot was completely removed during fibrinolysis, and there was no case of pulmonary emboli in CT angiography. The difference between two groups in terms of residual PTE was significant six months after the treatment.

Consistent with the present study, the one conducted by Masotti *et al.*, evaluated the PTE and pulmonary emboli with hereditary and acquired risk factors. There was a significant association between the emboli and hereditary risk factors (10).

In the study conducted by Masotti *et al.*, among the acquired risk factors providing PTE, the frequency of risk factor for surgery and long-term rest was high (10). However, among the group with acquired risk factors, surgery and trauma were the most prevalent acquired risk factors for pulmonary thromboembolism.

Based on the significant association between the hereditary risk factors and pulmonary emboli, by taking special measurements of prevention and treatment (e.g. genetic engineering), most of the pulmonary and mortality complications are prevented and the patient and health care system will benefit.

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