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Management of Acute Pulmonary Embolism: a Four-Year Study

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ABSTRACT

***Background**: Pulmonary embolism is one of the most common preventable causes of death in hospitalized patients and its related mortality and morbidity rate can be reduced considerably by proper treatment. It seems that there are some problems in treatment of acute pulmonary embolism in most health care centers.*

In this study, treatment of pulmonary embolism was evaluated in Tehran Imam Khomeini Hospital and compared with the standard therapy.

***Materials and Methods**: All records of patients hospitalized with the diagnosis of acute pulmonary embolism during four years (1998 to 2002) were examined thoroughly.*

Major points under the study are: Treatment with heparin regarding the dosage, time of performing Partial Thromboplastin Time (PTT) test during the treatment in order to determine the drug efficacy , modifying the drug dosage according to PTT results and prescribing oral anticoagulants.

***Results**: Fifty four patients with mean age of 51.3 years entered the study. Bolus dose of heparin was administered to 16 patients (29.6%). In regard to later infusion rates of heparin, only in 2 patients the prescribed dosage (3.7%) was in accord with one of the standard protocols and in the remaining, drug dosage was less than the recommended rate.*

Therefore, the optimal therapeutic range of heparin according to PTT in the first 24 hours of treatment was achieved only in 12 cases.(22.2%)

PTT was checked every 12 hours in one case and every 24 hours in 53 cases.

The mean treatment period with heparin was 9.9± 4.6 days.

The mean time of starting warfarin was 2.8± 2.3 days after heparin therapy and only 53.1% of the patients had International Normalized Ratio (INR) between 2 to 3 in two consecutive days at the time of discharge.

***Conclusion**: Results of this study indicate that physicians usually tend to use insufficient doses of heparin and delay in starting warfarin. Furthermore, evaluation of the therapeutic effects was not performed in any patient by repeated PTT test specially in the first 24 hours of treatment.*

According to the results of various studies this type of therapy leads to increased rate of relapse, mortality and morbidity due to pulmonary embolism. ***(Tanaffos 2004; 3(12): 49-51)***

***Key Words**: Pulmonary thromboembolism, Treatment, Heparin, Warfarin*

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INTRODUCTION

Pulmonary embolism is one of the most common preventable causes of death in the hospital (1, 2, 3) that in case of no treatment has a high mortality rate of about 30%.(4,5)

With approprite treatment its mortality and morbidity rate is decreased to 1-10 % (6, 7, 8).

Cause of death in these patients is largely due to repeated embolisms. Therefore, preventing its relapse by using anticoagulant drugs is one of the important objectives of the treatment.(8, 9, 10)

In most cases, treatment is started with heparin and the PTT level must reach to 1.5-2.5 times greater than the control rate as quickly as possible (9,10).

In fact, in the first 24 hours of starting heparin infusion, PTT must be checked repeatedly and heparin dose has to be adjusted accordingly.

If the PTT level is lower than the therapeutic range within the first 24 hours of treatment, the relapse rate of embolism will increase (11,12).

However, in many cases physicians prescribe inadequate doses of heparin in fear of bleeding, and consequently the expected PTT level can not be obtained (13).

In our health care centers, it is frequently seen that PTT has not reached the optimal level even few days after starting heparin.

On the other hand, in most cases, heparin infusion is not performed by pump and consequently alteration in the infusion rate is inevitable.

Starting warfarin therapy on time is another major point which is usually begun later than it should have been. Therefore, hospitalization period is increased. Whereas, warfarin can be prescribed either simultaneously or on the next day after starting heparin(13, 14).

In this study, with the aim of evaluating the treatment plan, we evaluated cases of pulmonary thromboembolism (PTE) in one of the largest educational centers in Iran during a 4-year period.We are hoping that by presenting the exact results we can put a step forward in modifying and improving the treatment plan of this disease.

MATERIALS AND METHODS

Under study population were all patients with the diagnosis of pulmonary embolism which were hospitalized and underwent treatment in Imam Khomeini Hospital in Tehran during the years 1998 to 2002. In performing this research, all medical records entitled by the codes related to pulmonary embolism (ICD.9.CM) were reviewed during the above mentioned years.

Inclusion criterion was the proven diagnosis of acute pulmonary thromboembolism based on clinical manifestations and paraclinical data (disregarding the methods of reaching the diagnosis) made by the physician. Exclusion criteria were as follows:

A) Discontinuation of the treatment during hospitalization (treatment period of less than 48 hours due to any reason such as misdiagnosis, death, etc.)

B) Receiving oral anticoagulant before the appearance of pulmonary embolism as the result of another underlying disease.

C) Records which were not assessable because they were imperfect or there was a doubt in diagnosis. Among the records which were noted down physician's orders, progress notes, nursing notes and test results were evaluated thoroughly and precisely and the obtained results were collected in special forms.

Since the aim of this study was the evaluation of the treatment plans, we did not investigate that how the physicians made the diagnosis. Only those documents indicating the definite diagnosis were accepted and the remaining were excluded from the study.

At the end, results obtained from the treatment

protocols and management effects in these patients were compared with the current and standard protocols which are mentioned below:

The standard treatment plan in stable PTE is to start heparin and warfarin simultaneously (13).

Heparin prescription dosage is based on one of the two methods below:

1-Therapeutic regimen including prescription of heparin 5000 units as bolus and then 40000 units per day as intravenous (IV) infusion (30000 units per day for patients with special conditions) (15).

2-Weight based therapeutic regimen includes 80 u/kg heparin as bolus and then 18 u/kg/h as intravenous infusion (16).

In regard to controlling the therapeutic effects PTT must be measured every 4 to 6 hours after starting infusion with each of the above mentioned methods. The drug dosage must be adjusted according to the PTT results to make PTT reach 1.5 to 2.5 times greater than its normal level, after that it has to be checked daily (15, 16).

Statistical analysis was performed using SPSS software.

RESULTS

During this 4 years period, there were a total number of 77 records with the codes of pulmonary embolism. Among those, 23 were excluded from the study considering the exclusion criteria. (Nine cases of discontinued treatment in the first 48 hours, 3 cases of receiving oral anticoagulant before the embolism occurred, 11 cases of incomplete records and doubt in diagnosis).

Therefore, records of 54 patients were evaluated thoroughly regarding the treatment plan. The mean age of patients was 51.3 years and 37% were male. The frequency of using diagnostic means included: perfusion scan in 92.6%, Doppler sonography of veins of lower extremities in 79.6%, D-dimer plasma measurements in 13% and pulmonary angiography in 1.9%. In all patients, treatment was with unfractionated heparin administered as IV. In one case, heparin was administered using pump and in the remaining cases microset was used.

Regarding the prescribed dosage of drug only two cases (3.7%) were consistent with one of the mentioned protocols that in one case 40000 units of heparin in 24 hours and in another case which had been operated one week before the embolism, 30000 units in 24 hours were prescribed. Meanwhile, in only one of the two cases, monitoring had been performed by performing 12 hours PTT. In the remaining 53 cases, PTT had been checked every 24 hours.The important points in treatment with heparin in these patients are listed in table 1.

Table 1. Important points in treatment with heparin in 54 patients under the study.

Prescription of bolus dose	16 (29.6%)
5000 units	13 (24%)
10000 units	3 (5.6%)
Method of repeated prescription of heparin	
Intermittent infusion	27 (50%)
Continuous infusion	27 (50%)
Heparin prescription dose (U/24h)	
Mean ± Standard deviation	23.440±2.630
Variation range	20000-40000
PTT every 6 hours within the first 24 hours	0
PTT every 12 hours within the first 24 hours	1
PTT every 24 hours	53
Optimal PTT within the first 24 hours of treatment with heparin	12 (22.2%)
Optimal PTT in whole treatment period	45 (83.3%)
Time of achieving the optimal PTT after starting heparin (day)	
Mean	3
Mean ± Standard deviation	3.8 ± 2.7
Variation range	0-12
Heparin prescription period	
Mean	9
Mean ± Standard deviation	9.9 ± 4.6
Variation range	3 - 21

Thrombolytic therapy, IVC filter and embolectomy each had been performed in one case as well. Low Molecular Weight heparin (LMWH) was not used in any of the patients.
Important points in regard to treatment with warfarin are listed in table 2.

Table 2. Important points in treatment with warfarin in 54 patients under the study.

Time of starting warfarin after staring heparin therapy (day)	
Median	3
Mean ± Standard deviation	2.8±2.3
Variation range	0-8
Primary warfarin dose (mg)	
Mean ± Standard deviation	4.6±2.1
Variation range	1.25-10
INR between 2 to 3 in two consecutive days before discontinuing heparin	23 (53.1%)
INR at the time of discharging	
Less than 2	33.6%
2-3	53.1%
More than 3	13.3%
Period of simultaneous use of heparin and warfarin (day)	
Median	6
Mean ± Standard deviation	6.8±4.0
Variation range	1-18

DISCUSSION

The standard anticoagulant regimen for treating PTE is simultaneous initiation of heparin and warfarin administration in all medically stable patients (13).

The best therapeutic regimen with heparin is continuous intravenous infusion until the PTT reaches 1.5 to 2.5 times greater than the control level (9, 10, 17, 18, 19).

Various studies have shown that a great part of the therapeutic effect of heparin is due to the fact that the optimal therapeutic range of heparin is achieved within the first 24 hours of therapy. On the other hand inadequate heparin therapy increases the chance of recurrent pulmonary embolism within 3 months after starting the treatment (11, 12).

Unfortunately, the results obtained from different studies have shown that the heparin dose prescribed by the physicians is usually less than the recommended dose (13, 20, 21).

To solve this problem standard protocols have been recommended earlier for prescription of heparin and subsequent monitoring of the treatment.

The aim of all these protocols is to reach the therapeutic concentration level of heparin in blood faster (15, 16, 22).

When using each of the recommended protocols, PTT values must be measured 4 to 6 hours after starting the infusion and the dosage of heparin must be adjusted accordingly.

PTT measurement must be repeated every 4 to 6 hours, till it reaches 1.5 to 2.5 times greater than the control level and then must be checked daily (15,16).

Therefore, the important point in choosing any therapeutic regimen is to adjust the drug dosage according to PTT results in order to reach the optimal PTT faster. In this study, it is clearly showed that the proper protocol for treatment of pulmonary embolism has not been followed in this center. In this center heparin bolus dose is prescribed only in 29.6% of the cases.

The optimal therapeutic range of heparin was obtained only in 22.2% of the cases in the first 24 hours. This fact indicates the insufficient dose of therapy.

In fact, majority of patients had received heparin according to the standard care nomogram (1000 u/h), and recent protocols which are proved to be better than the aforementioned ones had not been used (15, 16, 22).

Another point which is more important is that monitoring the efficacy of treatment had not been basically performed by repeated PTT test specially within the first 24 hours. This might be due to some limitations in laboratory work.

Other studies have also showed that many physicians of health care centers were not properly acquainted with the treatment protocols for pulmonary embolism. For example, in a retrospective study performed in an educational hospital in Croatia between the years 1997 and 1998 the aforementioned protocols were followed only in 15% of the cases and the optimal therapeutic range of heparin was achieved only in 17% of the cases (23).

Additionally, in another study performed on 65 patients with venous thromboembolism, the optimal therapeutic range of heparin in the first 24 hours had been obtained only in 40% of the patients (21).

It seems that the reasons for above mentioned problems in treating PTE in our country or in researches performed in other countries are due to prescribing insufficient doses of heparin, delay in obtaining PTT, not adjusting the heparin dose according to the PTT result, and most part of these problems are due to physicians fear of bleeding as a complication of heparin therapy (10).

It is noteworthy to state that although there is a strong correlation between lower than therapeutic levels of heparin and recurrent thromboembolism, the relation between higher than 2.5 times PTT levels and occurrence of bleeding is not proven and bleeding mostly depends on patients' underlying problems rather than the PTT level (10, 15).

There are some considerable problems in our study in regard to treatment with warfarin. The mean time of starting warfarin is 2.8 days after starting heparin and this is the cause of longer period of hospitalization and longer use of heparin.

Furthermore, INR between 2 to 3 for two consecutive days which is the appropriate time for discontinuing heparin is obtained at the time of discharging only in 53.1% of the patients, which is a considerable problem in treatment plan (24).

It seems that the treatment method of PTE in many health care centers in our country is the same as the one in our understudy center. Therefore, more attention must be paid in this regard.

We must notice that treatment with appropriate doses of heparin and precise monitoring of therapeutic effects during therapy, specially within the first 24 hours (which needs the cooperation and precision of laboratory personnel), and also noting the time of starting warfarin not only increases the clinical prognosis of pulmonary thromboembolism but also considerably decreases the hospitalization period and its related costs.

REFERENCES

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. ***Arch Intern Med*** 2003; 163 (14): 1711- 7.
2. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. ***Arch Intern Med*** 1991; 151 (5): 933- 8.
3. Dismuke SE, Wagner EH. Pulmonary embolism as a cause of death. The changing mortality in hospitalized patients. ***JAMA*** 1986; 255 (15): 2039- 42.
4. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. ***Lancet*** 1960; 1: 1309- 12.
5. Kanis JA. Heparin in the treatment of pulmonary thromboembolism. ***Thromb Diath Haemorrh*** 1974; 32 (2-3): 519- 27.
6. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on

Antithrombotic and Thrombolytic Therapy. ***Chest*** 2004; 126 (3 Suppl): 401S- 428S. Review. Erratum in: ***Chest*** 2005; 127 (1): 416.

7. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. ***JAMA*** 1998; 279 (6): 458- 62.
8. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. ***N Engl J Med*** 1992; 326 (19): 1240- 5.
9. Fedullo PF. Pulmonary thormboembolism. In: Murray JF, Nadel JA. Textbook of respiratory medicine. Third ed. Philadelphia: Sanders; 2000. p. 1503.
10. Valentine KA, Hull RD. Treatment of acute pulmonary embolism. Available at www.uptodate.com 2005; vol 13 No 1.
11. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. The emerging theme of delayed recurrence. ***Arch Intern Med*** 1997; 157 (20): 2317- 21.
12. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. ***Arch Intern Med*** 1997; 157 (22): 2562- 8.
13. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. ***Eur Heart J*** 2000; 21 (16): 1301- 36.
14. Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. ***Lancet***. 1986; 2 (8519): 1293- 6.
15. Hull RD, Raskob GE, Rosenbloom D, Lemaire J, Pineo GF, Baylis B, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. ***Arch Intern Med*** 1992; 152 (8): 1589-95.
16. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. ***Ann Intern Med***. 1993; 119 (9): 874- 81.
17. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. ***Chest*** 2001; 119 (1 Suppl): 176S- 193S.
18. Tai NR, Atwal AS, Hamilton G. Modern management of pulmonary embolism. ***Br J Surg*** 1999; 86 (7): 853- 68.
19. Goldhaber SZ. Pulmonary embolism. ***N Engl J Med*** 1998; 339 (2): 93- 104.
20. Fennerty AG, Thomas P, Backhouse G, Bentley P, Campbell IA, Routledge PA. Audit of control of heparin treatment. ***Br Med J (Clin Res Ed)*** 1985; 290 (6461): 27- 8.
21. Wheeler AP, Jaquiss RD, Newman JH. Physician practices in the treatment of pulmonary embolism and deep venous thrombosis. ***Arch Intern Med*** 1988; 148 (6): 1321- 5.
22. Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. ***Arch Intern Med*** 1991; 151 (2): 333- 7.
23. Vucic N, Lang N, Balic S, Pilas V, Anic T, Nadinic V, et al. Comparison between critical pathway guidelines and management of deep-vein thrombosis: retrospective cohort study. ***Croat Med J*** 2000; 41 (2): 163-7.
24. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. ***Chest*** 2001; 119 (1 Suppl): 8S- 21S.