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Comparison of low-molecular-weight-heparin and unfractionated heparin for acute PTE*

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Abstract: Objective: Acute pulmonary thromboembolism (PTE) is a serious high mortality pulmonary vascular disease whose effective treatment decreases morbidity and mortality. To determine if low-molecular-weight-heparin (LMWH) is clinically as efficient and safe as unfractionated heparin (UH) in patients with diagnosis of acute non-massive PTE, our study compares the efficacy, adverse effects and costs of LMWH and UH. Methods: One hundred and fourteen patients with non-massive acute PTE were randomly divided into LMWH (nadroparin calcium) and UH groups. Oxygenation index, D-dimer, fibrinogen (FG), lung ventilation/perfusion (V/Q) scan and computed tomography pulmonary angiography (CTPA) were observed before anticoagulation and on day 14 after anticoagulation. Results: In both groups, the ABG (arterial blood gas) analysis showed PaO_2 and $PaCO_2$ were elevated, $P(A\text{-}a)O_2$ was decreased and oxygenation index (PaO_2/FIO_2) was elevated, D-dimer and fibrinogen were decreased, lung V/Q and CTPA showed embolized segments reduced ($P<0.05$). Hemorrhage and thrombocytopenia occurred in 3.5% of the LMWH group. Hemorrhage occurred in 5.3% and thrombocytopenia occurred in 7.0% of the UH group. The average cost in the LMWH group was RMB 1218.60 Yuan and RMB 1541.40 Yuan in the UH group. Conclusion: LMWH and UH are equally effective for treatment of non-massive acute PTE, but LMWH may have a lower prevalence of complications and is less expensive.

Key words: Low-molecular-weight-heparin (LMWH), Unfractionated heparin (UH), Venous thrombosis
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INTRODUCTION

Acute pulmonary thromboembolism (PTE) is a serious pulmonary vascular disease with high mortality. The challenge is to make a correct diagnosis and give appropriate treatment (Nicolaides *et al*., 2001). Effective treatment will decrease morbidity and mortality. This study compares the efficacy, adverse effects and costs of low-molecular-weight-heparin (LMWH) and unfractionated heparin (UH).

MATERIALS AND METHODS

Materials

All patients diagnosed as non-massive acute PTE between September, 2000 to December, 2004 in our hospital were included. The total of 114 patients was randomly divided, 57 LMWH patients group and 57 UH patients group. The LMWH group had 35 males and 22 females, ages 33 to 74 average 50.40 years old. The primary diseases included fourteen with lower extremity deep venous thrombosis, nine chronic obstructive pulmonary disease, seven pneumonia, five cerebral infarction, four lung cancer, three post-operation hip replacement, three post C-section, three breast carcinoma, two interstitial pneumonitis, two Budd-chiary syndrome, two coronary atherosclerotic heart disease, two colon cancer and one without primary disease. The UH group had 33 males and 24 females, ages 23 to 75 average 53.65. The primary diseases included thirteen with lower extremity deep venous thrombosis, eight lung cancer,

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six chronic obstructive pulmonary disease, five post-operation hip replacement, four breast tumor, three coronary atherosclerotic disease, three esophageal cancer, three systemic lupus erythematosus, three colon cancer, three cerebral infarction, three upper extremity deep venous thrombosis, one fracture of left toes and two without primary disease. Diagnostic guidelines were shown in (Chinese Medical Association (Respiratory Branch), 2001).

Methods

LMWH group: Initially LMWH (nadroparin calcium) was injected subcutaneously 0.1 ml/10 kg q12h, then warfarin was added 24 h later. When the PT/INR reached 2.0 to 3.0 for 2 d, LMWH was discontinued. Warfarin was continued for another 3 months.

UH group: Initially the patient received a loading dose of 80 U/kg intravenously, the continuous IV infusion with dose titration according to APTT (activated partial thromboplastin time) results. Warfarin was started after the APTT reached 1.5 to 2.5 times control. UH was then discontinued when the PT/INR reached 2.0 to 3.0 for 2 d and warfarin was continued for 3 months as in the LMWH group.

During the anticoagulation period, the patient was periodically evaluated with ABG, D-dimer, fibrinogen (FG), lung V/Q scan, computed tomography pulmonary angiography (CTPA). These evaluations were performed before anticoagulation and repeated 14 d later to assess the patient's progress. We also monitored patients for hemorrhage, thrombocytopenia and assessed the cost.

Statistical analysis

Data are expressed as mean±standard error. Significance was determined with Student's test. A P value<0.05 was considered statistically significant.

RESULTS

Patient characteristics

This series of 46 female and 68 male patients had 57 patients in UH group and 57 in LMWH group. As shown in Table 1, there were no differences between the two groups for age, gender, oxygenation index, D-dimer, FG, embolized segments determined by V/Q or CTPA before anticoagulation. All 114 patients had relief of dyspnea, recovered and were discharged.

Efficacy of LMWH and UH

Fourteen days after treatment, both groups showed elevated PaO_2 and $PaCO_2$, $P(A\text{-}a)O_2$ decreased and oxygenation index (PaO_2/FIO_2) improved, there was decrease in D-dimer, FG and number of embolized lung segments as determined by both V/Q scan and CTPA (P<0.05, Tables 2 and 3). There was no significant difference in these parameters between LMWH and UH groups (P>0.05, Table 4).

Adverse effects of LMWH and UH

In the LMWH group, two patients had thrombo-

Table 1 PTE patients characteristics (n=114)

Characteristics	LMWH group (n=57)	UH group (n=57)	P
Age (years)	50.40±13.77	53.65±15.08	>0.05
Male/female	35/22	33/24	>0.05
Oxygenation index	320.20±110.52	281.45±118.30	>0.05
D-dimer (μg/ml)	8.89±8.03	10.06±9.75	>0.05
FG (g/L)	6.37±1.50	5.40±1.42	>0.05
*V/Q	3.60±1.18	3.90±1.25	>0.05
**CTPA	3.05±1.30	2.80±1.26	>0.05

*V/Q: Embolized segments determined by V/Q; **CTPA: Embolized segments determined by CTPA; All the data was collected before anticoagulation therapy

Table 2 Anticoagulation effects with LMWH

Observe time	Oxygenation index	D-dimer (μg/ml)	FG (g/L)	V/Q (segments)	CTPA (segments)
Before therapy	320.20±110.52	8.89±8.03	6.37±1.50	3.60±1.18	3.05±1.30
14 d after therapy	458.27±49.90	3.05±1.88	3.12±1.75	0.87±0.58	0.78±0.54
P	<0.01	<0.05	<0.05	<0.01	<0.01

cytopenia, two had hemorrhage; compli- cation rate was 3.5%. In the UH group there were four patients with thrombocytopenia and three with hemorrhage; complication rate was 7.0% and 5.3% respectively.

Cost of LMWH and UH

The cost of LMWH treatment (RMB 1218 Yuan) was significantly less than that of UH treatment (RMB 1541 Yuan) (P<0.05, Table 5).

DISCUSSION

Pulmonary thromboembolism continues to challenge physicians as it may frequently occur with atypical or in the absence of symptoms. It is a common and costly medical problem and is associated with significant morbidity and mortality (Holzheimer, 2004), but correct diagnosis is often missed (Deitcher and Carman, 2002). According to statistical data, PTE is responsible for approximately 150000 to 200000 deaths per year in the United States alone (Pineo and Hull, 1998) and the morbidity of PTE is increasing yearly in China, so we should pay more attention to pulmonary embolism.

With prompt diagnosis and anticoagulation therapy, PTE patients may have increased survival rate. Therapy with UH for PTE became widely accepted in the early 1960s while LMWH was used more often in the late 1980s (Buller, 2002). Clinically, LMWH and UH are the most common anticoagulants used for acute PTE nowadays (Valiukiene *et al*., 2003). Acute PTE treatment with subcutaneous LMWH or alternatively IV UH were recommended for treating confirmed non-massive PTE in the guideline in 2004 (Grade 1A) (Buller *et al*., 2004).

Many studies and increasing experience showed that LMWH is an effective drug to PTE. It was noted that LMWH was as effective as UH for treatment of PTE (McRae and Ginsberg, 2004; Moreno-Palomares *et al*., 2001; Davis and Faulds, 1997), while some other studies showed that LMWH was more effective than UH (Manganaro *et al*., 2000), but these conclusions was questioned. So we chose one kind of LMWH (nadroparin calcium) to treat the PTE patients for comparison with UH. The symptoms of dyspnea and chest pain being relieved in both groups indicated that anticoagulation therapy was effective. Moreover, our study showed elevated oxygenation index and decreased D-dimer and FG in both groups. The lung V/Q and CTPA showed reduction of embolized segments in both groups. There were no statistical differences between the two groups. Thus in our study LMWH was at least as effective as UH in the treatment of PTE.

Table 3 Anticoagulation effects with UH

Observe time	Oxygenation index	D-dimer (μg/ml)	FG (g/L)	V/Q (segments)	CTPA (segments)
Before therapy	281.45±118.30	10.06±9.75	5.40±1.42	3.90±1.25	2.80±1.26
14 d after therapy	424.10±52.60	3.51±2.12	2.48±1.60	1.10±0.63	0.85±0.52
P	<0.01	<0.05	<0.05	<0.01	<0.01

Table 4 Comparison of anticoagulation effects with LMWH and UH

Group (n)	Difference of oxygenation index	Difference of D-dimer (μg/ml)	Difference of FG (g/L)	Difference of V/Q (segments)	Difference of CTPA (segments)
LMWH (57)	138.07±70.03	5.84±4.40	3.25±1.55	2.73±0.60	2.27±0.65
UH (57)	142.65±85.40	6.55±4.95	2.92±1.25	2.80±0.66	1.95±0.58
P	>0.05	>0.05	>0.05	>0.05	>0.05

Table 5 Comparison of cost in anticoagulation therapy with LMWH and UH

Group (n)	Medication cost (RMB Yuan)	Injection cost (RMB Yuan)	Monitoring cost (RMB Yuan)	Total cost (RMB Yuan)
LMWH group (57)	1158.60±541.00	6.00±3.40	54.00±20.15	1218.60±549.50*
UH group (57)	69.70±29.05	866.00±284.50	605.70±308.45	1541.40±591.60

*P<0.05

The effectiveness of both UH and LMWH in treatment of PTE has been confirmed, although they are both associated with such complications as hemorrhage and thrombocytopenia (Eikelboom and Hankey, 2002; Marbet, 2003). Severe hemorrhage such as cranial hemorrhage may cause death. Many studies revealed that LMWH treatment of PTE resulted in less hemorrhage and thrombocytopenia than UH (McRae and Ginsberg, 2004; Marbet, 2003; Gylys, 2001). Although both may occurs in some cases (Ng and Lee, 2003). In our study treatment with LMWH resulted in hemorrhage in 2 patients (3.5%) and thrombocytopenia occurred in 2 patients (3.5%). The primary underlying disease of one hemorrhage patient who had GI (gastrointestinal) bleeding was lung cancer. Hemorrhage ceased after discontinuation of LMWH and there was no recurrence after resuming LMWH. In the UH group thrombocytopenia occurred in 4 patients (7.0%) and hemorrhage occurred in 3 other patients (5.3%). The platelet count increased without discontinuation of UH in the 4 thrombocytopenia patients. In the 3 hemorrhage patients, the bleeding occurred between day 3 and day 6 of therapy. The hemorrhage was controlled after discontinuation of UH. Our study indicates a possible advantage of LMWH over UH for complications of thrombocytopenia and hemorrhage. But probably due to the small number of patients in our study, statistically significant differences were not confirmed.

Some studies done to estimate the cost-effectiveness of low-molecular-weight-heparin (LMWH) in the treatment of PTE revealed that treatment with LMWH leads to savings as compared with UH in patients with PTE (Holzheimer, 2004; Estrada *et al*., 2000). Our study also considered the expense of LMWH treatment vs UH treatment. Included in this analysis were the costs of medications, injections, and monitoring lab tests. Although the medication cost of LMWH was higher, the injection and lab monitoring costs were less so that the total cost was less. In our study all patients were admitted to the hospital, although the safety of LMWH has allowed their treatment as outpatients (Wells and Buller, 2001; Wells, 2001), that could lower the cost even further.

In summary, both LMWH and UH are effective for treatment of PTE, although LMWH may have a lower prevalence of complications and is less expensive. What was more, the handling of LMWH is more comfortable for patients and less time consuming for nurses compared to UFH (Holzheimer, 2004), and it was found that routine laboratory monitoring was unnecessary (Manganaro *et al*., 2000; Messmore *et al*., 2004). So, LMWH may be better than UH in the treatment of PTE.

References

Buller, H.R., 2002. Treatment of symptomatic venous thromboembolism: improving outcomes. *Semin. Thromb. Hemost.*, **28**(Suppl 2):41-48. doi:10.1055/s-2002-32315.

Buller, H.R., Agnelli, G., Hull, R.D., Hyers, T.M., Prins, M.H., Raskob, G.E., 2004. Antithrombotic therapy for venous thromboembolic disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.*, **126**(3 Suppl):401S-428S.

Chinese Medical Association (Respiratory Branch), 2001. The guideline of diagnosis and treatment of PTE (draft). *Chin. J. Tuberc. Respir. Dis.*, **24**(5):273-275 (in Chinese).

Davis, R., Faulds, D., 1997. Nadroparin calcium. A review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs Aging.*, **10**(4):299-322.

Deitcher, S.R., Carman, T.L., 2002. Deep venous thrombosis and pulmonary embolism. *Curr. Treat Options Cardiovasc. Med.*, **4**(3):223-238.

Eikelboom, J.W., Hankey, G.J., 2002. Low molecular weight heparins and heparinoids. *Med. J. Aust.*, **177**(7):379-383.

Estrada, C.A., Mansfield, C.J., Heudebert, G.R., 2000. Cost-effectiveness of low-molecular-weight heparin in the treatment of proximal deep vein thrombosis. *J. Gen. Intern. Med.*, **15**(2):108-115. doi:10.1046/j.1525-1497.2000.03349.x.

Gylys, K.H., 2001. Pharmacology department. *J. Cardiovasc. Nurs.*, **15**(4):91-95.

Holzheimer, R.G., 2004. Low-molecular-weight heparin (LMWH) in the treatment of thrombosis. *Eur. J. Med. Res.*, **9**(4):225-239.

Manganaro, A., Giannino, D., Lembo, D., Bruni, F., Consolo, F., 2000. Evolution in the pharmacological treatment of venous thrombosis according to evidence-based medicine. *Minerva Cardioangiol.*, **48**(12 Suppl 1):41-51 (in Italian).

Marbet, G.A., 2003. Heparins. *Ther. Umsch.*, **60**(1):10-13 (in German).

McRae, S.J., Ginsberg, J.S., 2004. Initial treatment of venous thromboembolism. *Circulation*, **110**(9 Suppl 1):I3-I9. doi:10.1161/01.CIR.0000140904.52752.0c.

Messmore, H.L., Covne, E., Wehrmacher, W.H., Demir, A.M., Fareed, J., 2004. Studies comparing low molecular weight heparin with heparin for the treatment of thromboembolism: a literature review. *Curr. Pharm. Des.*, **10**(9):1001-1010. doi:10.2174/1381612043452802.

Moreno-Palomares, J.J., Fisac-Herrero, R.M., Herrero-Domingo, A., Ferreira-Pasos, E.M., Grasa, J., Reverte-Cejudo, D., 2001. Low molecular weight heparin versus unfractionated heparin in the treatment of deep vein thrombosis. *An. Med. Interna.*, **18**(7):364-368 (in Spanish).

Ng, H.J., Lee, L.H., 2003. Heparin-induced thrombocytopenia: acknowledging its presence in low-molecular weight heparin therapy. *Int. J. Hematol.*, **77**(2):185-187.

Nicolaides, A.N., Breddin, H.K., Fareed, J., 2001. Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. *Int. Angiol.*, **20**(1):1-37.

Pineo, G.F., Hull, R.D., 1998. Heparin and low-molecular-weight heparin in the treatment of venous thromboembolism. *Baillieres. Clin. Haematol.*, **11**(3):621-637.

Valiukiene, L., Naudziunas, A., Unikauskas, A., 2003. Treatment and prophylaxis of deep venous thrombosis with low molecular weight heparins (meta-analysis of clinical trials). *Medicina (Kaunas)*, **39**(4):352-358 (in Lithuanian).

Wells, P.S., 2001. Outpatient treatment of patients with deep-vein thrombosis or pulmonary embolism. *Curr. Opin. Pulm. Med.*, **7**(5):360-364. doi:10.1097/00063198-200109000-00019.

Wells, P.S., Buller, H.R., 2001. Outpatient treatment of patients with pulmonary embolism. *Semin. Vasc. Med.*, **1**(2):229-234. doi:10.1055/s-2001-18492.