Multicenter, Prospective Study Comparing Enoxaparin with Unfractionated Heparin in the Treatment of Submassive Pulmonary Thromboembolism

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OBJECTIVE: To compare the safety and efficacy of enoxaparin and unfractionated heparin in the treatment of submassive pulmonary thromboembolism (PTE).

MATERIAL AND METHODS: Fifty-six patients with PTE who did not need fibrinolytic treatment were enrolled prospectively. The patients were randomly assigned to 2 treatment groups: Group A received enoxaparin (1 mg/kg every 12 hours) and Group B received adjusted doses of unfractionated heparin. The oral anticoagulant therapy was started on confirmation of the diagnosis and continued for 6 months. Incidences of recurrence of thromboembolism and of severe bleeding were assessed at the end of this period.

RESULTS: Six patients were withdrawn from the study. Twenty-nine of the 50 remaining patients were in Group A (enoxaparin) and 21 in Group B (unfractionated heparin). A recurrence of thromboembolism was diagnosed in 3 patients from Group A (10.7%) and 2 patients from Group B (9.5%). There were no significant differences. Two patients died, one death being attributed to bleeding secondary to the oral anticoagulant treatment (Group A) and the other to a process unrelated to PTE.

CONCLUSIONS: Enoxaparin seems to be as effective and safe as unfractionated heparin in the initial treatment of PTE.

Key words: *Pulmonary thromboembolism. Heparin: unfractionated, low molecular weight. Enoxaparin.*

Estudio multicéntrico, prospectivo, de comparación del tratamiento de la tromboembolia pulmonar submasiva con enoxaparina y heparina no fraccionada

OBJETIVO: Evaluar la eficacia y seguridad del tratamiento de la tromboembolia pulmonar submasiva (TEP) con enoxaparina en comparación con heparina no fraccionada.

PACIENTES Y MÉTODOS: Se incluyó en el estudio, de forma prospectiva, a 56 pacientes con TEP que no precisaron tratamiento fibrinolítico. Se asignaron de forma aleatoria a dos grupos de tratamiento: el grupo A, que recibió enoxaprina (1 mg/kg cada 12 h) y el grupo B, al que se le administraron dosis ajustadas de heparina no fraccionada. La anticoagulación oral se inició una vez que el diagnóstico se comprobó y se mantuvo durante 6 meses. Se evaluó la incidencia de recurrencia tromboembólica y de hemorragia mayor al cabo de ese tiempo.

RESULTADOS: Seis pacientes fueron excluidos del estudio. De los 50 finalmente incluidos, 29 fueron asignados al grupo A (enoxaparina) y 21 al grupo B (heparina no fraccionada). Tres pacientes del grupo A (10,7%) fueron diagnosticados de recurrencia tromboembólica, mientras que dicha complicación se constató en dos pacientes del grupo B (9,5%). No se encontraron diferencias significativas. Dos pacientes fallecieron, siendo una de las muertes achacada a hemorragia secundaria a la anticoagulación oral (grupo A) y la otra a un proceso independiente a la enfermedad tromboembólica.

CONCLUSIONES: El empleo de enoxaparina en el tratamiento inicial del TEP parece ser tan efectivo y seguro como el uso de heparina no fraccionada.

Palabras clave: *Tromboembolia pulmonar. Heparina no fraccionada. Heparina de bajo peso molecular. Enoxaparina.*

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Introduction

Before the appearance of low molecular weight heparins (LMWH), unfractionated heparins (UFH) were used to achieve anticoagulation during the acute phase of venous thromboembolism (VTE). The use of LMWH

preparations can greatly simplify the treatment of VTE as administration is subcutaneous, at fixed dosage, and does not require laboratory monitoring except during pregnancy or in cases of renal insufficiency when anti-Xa activity should be measured. This, together with the fact that treatment can be followed at home, makes the cost/benefit ratio of LMWH superior to those of UFH.[1]

The efficacy and safety of LMWH in the treatment of deep vein thrombosis (DVT) has been demonstrated in a large number of studies. Some meta-analyses have even shown LMWH to be safer and more effective than UFH in this context.[2] There is less scientific evidence regarding pulmonary thromboembolism (PTE), although studies have been published that show at least an equivalent level of safety and efficacy between LMWH and UFH.[3-8] However, those studies have been carried out with different compounds (fraxiparine,[3] dalteparin,[4,8] reviparin,[5] and tinzaparine[6,7]) and a variety of treatment regimens—once or twice a day—and the results obtained may not be true for each and every LMWH.[9,10] We performed a multicenter, prospective, randomized trial to discover whether enoxaparin is as safe and effective as UFH in the initial treatment of thromboembolism.

Patients and methods

This was a multicenter, prospective open study, where enoxaparin (1 mg/kg every 12 hours) was compared with UFH in the treatment of submassive PTE. The protocol included objective diagnosis of PTE and DVT and was approved by the Ethics Committee of the Galician Public Health Service (SERGAS). The study was carried out in 3 Spanish hospitals: the Hospital Xeral–Calde in Lugo, the Hospital Comarcal in Monforte, and Complejo Hospitalario in Pontevedra.

The patients enrolled in the study were over 18 years old, were diagnosed with PTE, gave written informed consent, and had none of the following exclusion criteria: previous episode of DVT, PTE with hemodynamic repercussion, known factor of hypercoagulability, anticoagulant treatment, pregnancy, formal contraindication for anticoagulation or serious concomitant illnesses.

The patients were randomized from the lists of enrolled patients at each center using the SAS statistics program. All patients underwent a ventilation-perfusion scan within 24 hours and plethysmography of the lower extremities. Intraluminal filling defect in 2 or more projections or a sudden cutoff in a section of the deep vein system was considered proof of DVT. A PTE diagnosis was accepted if the results of the ventilation-perfusion scan were classified as "highly probable" following the Prospective Investigation of Pulmonary Embolism Diagnosis criteria[11] or if the arteriography was positive. Arteriography results were only considered positive if there was presence of an intraluminal filling defect in 2 projections and evidence of occlusion of a pulmonary artery. A PTE diagnosis was also accepted in patients with positive plethysmography and compatible conditions without evidence of other pulmonary disease that could cause the symptoms although the results of the scan were not "highly probable." If the scan results were normal, a PTE diagnosis was ruled out.

Patients were assigned to 1 of 2 treatment groups: Group A who were administered enoxaparin, 1 mg/kg weight every 12 hours, and Group B, who were administered 5% sodium heparin (Laboratorios Farmacéuticos ROVI, Madrid, Spain) and received an initial bolus dose of 5000 IU through an infusion pump (IVAC 5910®, IVAC CORP, San Diego, CA, USA), which was adjusted according to the partial thromboplastin time results to an approximate dose of 35 000 IU /day. When diagnosis of PTE was confirmed and no other diagnostic tests were needed, oral anticoagulation with acenocoumarol was started. Both treatments were continued simultaneously until an international normalized ratio (INR) of 2–3 was reached. Controls were programmed at 1, 3, and 6 months after hospital discharge to examine the clinical evolution and evaluate whether anticoagulation was sufficient (INR >2 in over 70% of controls). Patients were instructed to report to the hospital at any sign of a new episode of DVT or PTE. Recurrence was considered confirmed if the perfusion scan showed perfusion defects that had not existed in the initial exploration, if the arteriography showed new intraluminal filling defects, if the plethysmography showed a new venous region affected, or if there was a proximal thrombus extension of over 5 cm. Bleeding was considered "major" when it was intracranial, retroperitoneal, needed transfusion or when hemoglobin decreased by 2 or more points.

Statistical analysis

The mean and standard deviation and percentage for qualitative variables were used for the descriptive statistical analysis. Continuous variables of the patients of the 2 groups were compared using the Student *t* test or the Mann–Whitney test depending on the distribution of the variable. Qualitative variables were compared between the groups using the Fisher´s exact test.

Results

Fifty-six patients with PTE were enrolled in the study. Six patients were withdrawn, 2 for incorrect diagnosis, 2 for antecedents of venous thromboembolism, and 2 more were lost to follow-up. The 50 remaining patients (34 men and 16 women with a mean [SD] age of 66.2 [16.1] years), were assigned to receive enoxaparin

TABLE 1
Patient characteristics according to treatment group

Characteristics	Group A (enoxaparin)	Group B (UFH)
Sex		
Male	20 (69%)	14 (66.7%)
Female	9 (31%)	7 (33.3%)
Age, years (SD)	66.5 (16.2)	65.9 (16.3)
Temporary predisposing factor	13 (44.8%)	9 (42.9%)
Presence of DVT	7/29 (39%)	12/21 (71%)
PaO_2 (SD)	60.6 (15.0)	63.5 (11.5)
$D(A–a)O_2$ (SD)	43.9 (15.5)	40.7 (14.7)
Respiratory rate (SD)	21.6 (6.1)	20.2 (6.8)
SAP (SD)	134 (21.8)	136.9 (25.1)
S1Q3T3	3 (18.8%)	5 (35.7%)
Abnormal thorax radiograph	18 (62.1%)	9 (42.9%)

UFH indicates unfractionated heparin; DVT, deep vein thrombosis; $D(A–a)O_2$, alveolar-arterial oxygen tension difference; SAP, systolic arterial pressure.

TABLE 2
Risk factors according to treatment groups

Type of factor	LMWH		UFH	
	Number	Percentage	Number	Percentage
Traumatism	2	16.7	2	28.6
Surgery	4	33.3	2	28.6
Immobilization through illness	4	33.3	3	42.9
State of hypercoagulability	1	8.3	-	-
Traumatism and surgery	1	8.3	-	-
Total	12	100.0	7	100.0

LMWH indicates low molecular weight heparins; UFH, unfractionated heparins.

TABLE 3
Distribution of defects found in pulmonary scan, arteriography and plethysmography, according to treatment group

	LMWH		UFH	
	Number	Percentage	Number	Percentage
Defects in the scan				
Defect in lobe perfusion	7	24.1	7	33.3
Defect in segmentary perfusion	5	17.2	2	9.5
Two or more segmentary defects	17	58.6	12	57.2
Total	29	100.0	21	100.0
Defects in the arteriography				
Defects in periphery perfusion	-	-	1	16.7
Main branch of the PA	4	33.3	2	33.3
Lobar branch of the PA	8	66.7	2	33.3
Segmental branch of the PA	-	-	1	16.7
Total	12	100.0	6	100.0
Defects in the plethysmography				
Venous thrombosis				
Unilateral	5	83.3	8	88.9
Bilateral	1	16.7	1	11.1
Venous thrombosis				
Proximal	5	100.0	8	80.0
Sural	-	-	2	20.0
Normal	22	71.0	9	29.0

With the arteriography and the plethysmography, more than 1 defect can occur in the same patient. LMWH indicates lower molecular weight heparin; UFH, unfractionated heparin; PA, pulmonary artery

(Group A, n=29) or UFH (Group B, n=21). The clinical characteristics of the study population are summarized in Table 1. No significant differences between the groups were found for age (*P*=.783), sex (*P*>.999), presence or absence of predisposing factor (*P*>.999), respiratory rate (*P*=.286), systolic blood pressure (*P*=.661) electrocardiogram abnormalities (*P*=.768), PaO_2 (*P*=.710) or radiological irregularities (*P*=.252). Predisposing factors are shown for both treatment groups in Table 2. In Group A, 29% of patients were diagnosed with DVT, compared with 71% in Group B, which was a significant difference (*P*=.030). Arteriographies had to be performed on 10 patients from Group A and 6 from Group B. The location and extent of the defects found in the scan, arteriography, and plethysmography are shown in Table 3.

Recurrent thromboembolism was diagnosed in 3 patients from Group A (10.7%) and 2 patients from Group B (9.5%) (Table 4). No significant differences were found between the 2 groups (*P*=.878). The

TABLE 4
Recurrences, major bleeding, and death in the study patients, according to treatment group

Event and moment it occurred	Group A (enoxaparin)	Group B (UFH)
Recurrence		
Hospital admission	0	0
Hospital admission–1 month	3	2
1–3 months	0	0
3–6 months	0	0
Total	3 (10.7%)	2 (9.5%)
Major bleeding		
Hospital admission	1	0
Hospital admission–1 month	0	0
1–3 months	0	0
3–6 months	0	0
Total	1	0
Death		
Hospital admission	2	0
Hospital admission–1 month	0	0
1–3 months	0	0
3–6 months	0	0
Total	2 (6.89%)	0 (0%)

recurrence was pulmonary in all cases and occurred between hospital discharge and the first revision 1 month later. No patient died from a recurrence. Recurrence coincided with anticoagulation below the therapeutic range (INR<2) in only 1 case, which was from group B.

Two patients died, both from Group A. One death was caused by pulmonary aspergillosis and occurred during the initial hospitalization. The other occurred 7 days after enrollment in the study, from hypovolemic shock attributed to a massive retroperitoneal hemorrhage secondary to the oral anticoagulation (Table 4). This was the only episode of major bleeding recorded throughout the study. Table 4 details the number of recurrences, hemorrhages and deaths in both groups during the study.

Mean time of hospitalization was 10.4 days in Group A and 10.2 days in Group B (*P*=.903).

Discussion

Despite the fact that LMWH are replacing UFH for the initial treatment of DVT, they are compounds of different molecular weights, with different affinities for plasma proteins, different plasma half-lifes and varying factor Xa and thrombin inhibitory activities. Our study compared the efficacy and safety of enoxaparin and UFH in the initial treatment of submassive PTE. Patients were divided into 2 groups according to the initial treatment. The groups were comparable in age, sex, presence or absence of a temporary risk factor (immobilization), and PaO_2 on enrollment. Our study (in which the mean age was 66 years) enrolled significantly more men than women, a pattern which is not in keeping with the findings of Stein et al[12] who found that among patients aged over 50 years the incidence was higher for women. It should also be pointed out that there was a significantly larger number of patients with DVT in the UFH treatment group, probably by chance. Some studies indicate an increased risk of recurrence in patients with proximal DVT at the moment treatment starts,[13] but our study did not.

Five episodes of recurrence were recorded in our study: 3 in the enoxaparin group and 2 in the UFH group. The patients concerned (4 women and 1 man) had a mean age of 66 (range 44–80), and in 4 of the 5 cases there was a prior predisposing factor (surgery or injury). This notable prevalence of temporary risk factors differed from the published data,[14] where the subgroup of patients with such risk had a lower percentage of recurrence (1.4%) with respect to the subgroup of idiopathic VTE patients (6.7%). Our results offer a similar recurrence percentage for both treatment groups: 10.7% for Group A and 9.5% for Group B (*P*=.878). All the recurrences were pulmonary, happened between the initial hospitalization and the first revision (1 month), and were diagnosed according to strict criteria. In all cases patients were receiving oral anticoagulation and no recurrence caused death. These percentages are higher than those published in the Columbus study[5] (5.9% of recurrence with reviparin), in the Simmoneau et al study[6] (1.6% with tinzaparin), and in the Hull et al study[7] (no recurrence with tinzaparin) and is among the highest found in other studies.[15,16] The recurrences cannot have been due to inadequate oral anticoagulation (INR<2) as this only occurred in 1 patient. Length of treatment (4–7 days) with enoxaparin or UFH was similar to usual regimens and does not seem to have affected recurrence, and it is unlikely that the use of enoxaparin to treat PTE could have been the cause as the percentage of recurrence was not significantly different with enoxaparin and UFH treatment.

While it is true that the use of LMWH reduces costs, avoiding hospitalization or shortening hospital stays,[1,8] we did not find significant differences in the latter, given that our study was designed to have 2 treatment groups with similar characteristics.

The main limitation of this study was the number of patients enrolled, too few to make definite conclusions. However, the results agree with those already published and we consider enoxaparin to be a safe, effective initial treatment for patients with PTE.

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