Background: The risk-benefit ratio of early vs late heparinization for acute stroke with nonvalvular atrial fibrillation remains unsettled.

Objective: To clarify the relationship between timing to heparinization and functional outcome in acute cardioembolic stroke.

Design: Consecutive case series.

Setting: Referral center.

Patients: In 231 patients with stroke and nonvalvular atrial fibrillation, intravenous or subcutaneous heparin administered with the goal of achieving an activated partial thromboplastin time (APTT) 1.5 to 2.0 times control values. Delay to the initiation of heparin therapy was less than 6 hours from the onset of symptoms in 74 patients and between 6 and 48 hours in 157 patients. Functional outcome (Rankin scale) was assessed 9 ± 3 (mean ± SD) days from stroke onset using multivariate analysis and including in the model treatment delay, risk factors (eg, age, hypertension, diabetes, hypercholesterolemia, previous stroke, and heart disease), initial neurological severity, and baseline computed tomographic findings (eg, early signs of infarction and white matter abnormalities). Clinical symptoms on admission (Mathew score) and baseline radiological findings were evaluated in all subjects. The bleeding rate was assessed on subsequent computed tomographic (CT) scans (obtained 7 ± 2 days after stroke). The relationship between APTT ratios and stroke recurrence or hemorrhagic worsening was also tested.

Main Outcome Measures: Functional outcome at hospital discharge and incidence of early recurrent strokes and bleeding complications.

Results: Mortality (9%), hemorrhagic worsening (3.4%), and early stroke recurrence (2.1%) occurred in the hospital. Complete recovery was associated with age younger than 70 years (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.05-0.70), a baseline Mathew score higher than 74 (OR, 11.5; 95% CI, 4.95-26.70), normal baseline CT findings (OR, 8.86; CI, 3.99-19.60), and early heparinization (OR, 1.7; 95% CI, 1.10-2.50). Targeted APTT ratios were achieved at 24 hours in fewer than 50% of patients. Whereas stroke recurrence was associated with lower mean APTT ratios, higher mean APTT ratios were observed in patients with symptomatic bleeding, especially on the day of bleeding. Age, admission stroke severity, blood pressure, and baseline CT findings did not predict hemorrhagic worsening.

Conclusions: Delaying anticoagulation in alert patients with stroke and nonvalvular atrial fibrillation is not endorsed by the initial severity of symptoms or the early signs of infarction on CT scan. Functional recovery is improved the sooner heparin is administered. These findings suggest that heparin also has therapeutic properties. However, close APTT monitoring is warranted to lessen the incidence of untoward complications.

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The timing of heparin use in patients with stroke and nonvalvular atrial fibrillation (NVAF) remains a matter of preference of the treating physicians according to their estimation of the relative risk of early recurrent stroke vs that of hemorrhagic complications if anticoagulation is performed.1,2 Current guidelines recommend early anticoagulation only for patients at higher risk of recurrence if the infarction is not large, whereas delaying anticoagulation for several days to a week is preferred for patients at relatively low risk for early recurrence.3 However, therapeutic decisions in daily practice are complicated by the unclear risk of early recurrence in patients with stroke and NVAF.3

Unfortunately, the largest clinical trial that has prospectively evaluated the role of heparin in patients with acute stroke included patients with noncardioembolic strokes, and it is unknown whether the rate of untoward events was correlated with the biological effect of heparin, as indicated by the activated partial thromboplastin time (APTT).3 Other studies have suggested that an excessive level of anticoagulation, rather than the size of the infarction, explains most of the risk of hemorrhagic worsening in patients with thromboembolic stroke.3

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PATIENTS AND METHODS

From December 1993 to December 1996, a total of 231 consecutive stroke patients with NVAF or a history of NVAF (ie, absent P waves and a irregular ventricular response on the electrocardiogram) underwent anticoagulation as soon as a computed tomographic (CT) scan of the brain had ruled out a hemorrhagic infarction. Patients with rheumatic valve disease, dilated myocardioapathy, septic or nonseptic endocarditis, valve replacement, thyroid disease, decreased alertness, or seizures, or individuals participating in acute stroke therapeutic trials, were not included in the study. Baseline neurological impairment was classified as major stroke if the Mathew score (normal, 100) was 74 or lower. Otherwise, stroke was defined as mild to moderate. All studied patients underwent a cardiac examination, blood pressure measurements, standard blood tests, chest roentgenography, electrocardiography, and a brain CT scan prior to anticoagulation. Radiological variables of interest included the identification and topography of early signs of infarction, which referred to the lack of distinction between white and gray matter, or slight low attenuation involving subcortical structures and/or cortex and/or effacement of sulci. Coexistent patchy or diffuse low-attenuation abnormalities in the deep white matter were also evaluated. Second CT or MRI scans were obtained in all cases 7 ± 2 days after stroke onset or at any time if clinical symptoms worsened. Hemorrhagic worsening was defined in all patients in whom there was clinical deterioration and any degree of hyperdensity within the brain parenchyma on CT scans. Whereas hemorrhagic infarction included mottled or gyrfiform areas of increased density within an area of hypodensity, parenchymal hematomat was defined as homogeneous, dense signals within the area of infarction. Major extracranial hemorrhages that required transfusion were also classified as hemorrhagic worsening. Early recurrent stroke was defined as a cerebral ischemic event subsequent to the initial stroke that clearly resulted in a new deficit while the patients were in the hospital. Worsening of previous deficits was classified as worsening stroke. Carotid and vertebral Doppler ultrasonography or magnetic resonance angiography was performed to assess intracranial and extracranial atherosclerosis. Echocardiography was restricted to those patients in whom the medical history and physical examination findings were considered insufficient to rule out underlying heart disease. Depending on the preferences of the responsible physician, the patients received either 1000 IU/h of intravenous unfractionated heparin targeted at maintaining an APTT 1.5 to 2 times control values (n = 171) or 12,500 U of subcutaneous heparin every 12 hours (n = 60) for 5 to 10 days, until a stable degree of oral anticoagulation was achieved. Treatment was initiated as soon as a brain CT scan ruled out the presence of hemorrhagic infarction. Weight-based nomograms for heparin administration were not calculated and initial intravenous boluses of heparin were avoided to decrease the risk of bleeding complications. Monitoring of the APTT was initiated 6 ± 2 hours after heparin infusion and then repeated as needed according to the adequacy of APTT ratios (the APTT of the patient divided by the APTT of a healthy control). Additional therapeutic measures included careful management of fluid intake, blood pressure and serum glucose levels, nutrition, and temperature, as well as early mobilization and physical rehabilitation. Functional status was measured with the modified Rankin scale 9 ± 2 days from stroke onset and classified as “independent” (Rankin score, 0 to 1) or “dependent” (Rankin score, 2 to 6).

The following risk factors were considered: age (<60 years, 60-70 years, and >70 years), sex, history of hypertension (treated or blood pressure reading >160 mm Hg systolic or >90 mm Hg diastolic), diabetes (treated or fasting glucose level >6.1 mmol/L [>110 mg/dL]), hypercholesterolemia (treated or cholesterol level >6.21 mmol/L [>240 mg/dL]), previous stroke, and heart disease (history of myocardial infarction, angina pectoris, or congestive heart failure). The pattern of NVAF was further classified as chronic, paroxysmal, or recent-onset by personal interviews with patients or proxies and by review of medical charts from previous hospital admissions when available. The delay to anticoagulation was classified as more or less than 6 hours from the onset of symptoms. Overall, initiation of heparin therapy was delayed 15.2 ± 13.1 hours (range, 1-48 hours). Seventy-four patients (32%) underwent anticoagulation within 6 hours from the onset of symptoms and 157 patients (68%) after 6 hours (6-48 hours).

For statistical analysis of variables related to clinical outcome, categorical variables were analyzed with the use of χ2 tests, crude odds ratios (ORs) with 95% confidence intervals (CIs), and the t test for continuous variables. Stepwise forward logistic models were run to evaluate the independent contribution of variables with a P value of <.05 on univariate analysis. A level of .05 was established as statistically significant.

Recent studies suggested that besides its antithrombotic effects heparin also modulates the secretory activity of human monocytes, suppresses the activation of the complement system, and exerts anti-inflammatory activities, including the inhibition of cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor α. Since cytokine-mediated inflammation has been related to the severity of stroke, it could be argued that besides its prophylactic role heparin also has “therapeutic” effects resulting from the modulation of these inflammatory pathways. The present observational study was aimed at evaluating in a series of patients with stroke and NVAF who underwent anticoagulation whether the extent of functional recovery at hospital discharge was correlated with the delay to heparin administration. Also, it evaluated whether the incidence of recurrent strokes and hemorrhagic complications were related to the targeted biological effect of heparin.

RESULTS

The main characteristics of patients at hospital admission are described in Table 1. One hundred thirty-three patients (58%) were admitted with a major stroke (Mathew score ≤74), and 98 patients (42%) were admitted with a minor to moderate stroke. No significant
differences in main risk factors, baseline neurological score, or initial CT scan findings were found to be associated with the delay to treatment initiation. Age older than 70 years (OR, 3.7; 95% CI, 1.2-11.2), detection of early signs of infarction on CT scan (OR, 2.4; 95% CI, 1.4-4.3), and history of hypertension (OR, 1.7; 95% CI, 1.01-2.95) were associated with a more severe stroke at baseline, although using logistic regression analysis, only age older than 70 years (OR, 3.78; 95% CI, 1.2-11.2) remained independently associated with stroke severity.

Whereas 167 patients (72%) had some degree of functional impairment (Rankin score, 2 to 6) at discharge, including 21 patients (9%) who died, 64 patients (28%) had regained full independence (Rankin score, 0 to 1). Using logistic regression analysis, age older than 70 years (OR, 0.2; 95% CI, 0.05-0.7) was a negative predictor of functional recovery. Conversely, positive predictors of recovery included a Mathew score greater than 74 (OR, 11.5; 95% CI, 4.9-26.7), a baseline CT scan without signs of ischemic infarction (OR, 8.8; 95% CI, 3.9-19.6), and a delay to heparin administration of less than 6 hours (OR, 1.7; 95% CI, 1.1-2.5), respectively. Therefore, younger patients with less neurological impairment on admission and normal baseline CT findings had a greater chance of recovery, as did patients treated with heparin within 6 hours from the onset of symptoms.

Overall, the mean ± SD APTT ratio achieved among patients treated with intravenous heparin was 1.6 ± 0.7 compared with 1.4 ± 0.7 among patients treated with subcutaneous heparin (P = .02). The proportion of therapeutic and excessive APTT ratios at 24 hours from treatment initiation also differed according to the administration route. Thus, whereas 49% of patients treated with intravenous heparin reached therapeutic APTT ratios, 33% had achieved excessive APTT ratios. In the group of patients treated with subcutaneous heparin, these figures were 43%, and 14%, respectively.

Major clinical events during hospitalization included 5 recurrent strokes (2.16%) and 8 symptomatic episodes of bleeding (3.4%) (6 fatal and 2 nonfatal). Hemorrhagic worsening was associated with the development of parenchymatous hematoma in 5 patients and with systemic bleeding in 1 patient. On one hand, patients with early recurrent stroke had significantly lower mean APTT ratios than did patients without recurrent events (1.2 ± 0.2 vs 1.6 ± 0.4, P = .02). On the other hand, patients with hemorrhagic worsening during the treatment course had higher mean APTT ratios than did those without symptomatic bleeding (2.1 ± 0.7 vs 1.6 ± 0.7, P < .01). The greatest differences were observed when comparisons were restricted to APTT ratios obtained the day of bleeding (2.8 ± 0.8 vs 1.6 ± 0.7, P < .001). As shown in Table 2, hemorrhagic worsening was not associated with pretreatment stroke severity, age, treatment delay, admission blood pressure levels, history of hypertension, early detection of signs of infarction on CT scan, or coexistence of periventricular white matter abnormalities.

Every trial of heparin or heparinoids in acute stroke has failed to demonstrate a convincing benefit from this therapy. However, unresolved questions about the role of early anticoagulation in some stroke subtypes, such as stroke with NVAF, call for the reassessment of factors related to early stroke recurrence, hemorrhagic worsening, and functional outcome in this population. In the present observational study, we assessed patients with the same type of stroke who received a similar intensity of care regardless of their age and baseline stroke severity. Patients with seizures or decreased level of consciousness were excluded because of the difficulties in detecting worsening symptoms in these patients. Delay to anticoagulation only depended on the time that it took the patients to arrive at the hospital and to undergo a brain CT scan to rule out the presence of blood within the brain. A notable finding of the study was that low and high APTT ratios were related to stroke recurrence and hemorrhagic worsening, respectively. More importantly, the delay to initiation of heparin therapy was an independent predictor of functional recovery at hospital discharge, a
finding that is in agreement with the findings of studies that emphasized the relevance of acute stroke management. At baseline examination, patients who received heparin less than 6 hours from the onset of symptoms had the same degree of neurological impairment as patients who were treated after 6 hours. Therefore, the greater recovery rate that was observed in the group that was treated earlier could be attributed to the prompt initiation of treatment. Finally, we also confirmed the contribution of age and baseline clinical and CT findings to the likelihood of functional recovery, and the absence of correlation between pretreatment stroke severity and the risk of hemorrhagic worsening whenever the APTT ratios were maintained within therapeutic ratios.

Heparin represents the first-choice therapy for stroke with NVAF for many physicians, especially if the acute infarction is not large and the patient does not have uncontrolled hypertension. In patients with stroke and NVAF, the International Stroke Trial found 21 fewer recurrent ischemic strokes per 1000 patients treated with heparin (2.8% vs 4.9%), but this was offset by 16 more hemorrhagic strokes (2.1% vs 0.4%). Unfortunately, APTT monitoring was optional in this large study and no data were reported on the possible association between untoward complications and the degree of anticoagulation in patients treated with heparin. Moreover, the overall benefit of heparin for the prevention of early recurrent stroke in subjects with NVAF depends on the coexistence of risk factors, as a greater incidence of early recurrent events has been found in patients with additional risk factors. Thus, as demonstrated by Sacco et al., while the global risk of recurrence for cardioembolic infarction was estimated at 4.3%, the risk increased to 8.5% when hypertension and hyperglycemia coexisted. Since we did not find an association between the presence of vascular stroke risk factors and the risk of bleeding, it can be anticipated that patients with NVAF and additional risk factors will derive additional benefit from treatment with heparin. Of course, this conclusion does not preclude that adequate management of hypertension and hyperglycemia in the early phase of stroke might also result in a reduced incidence of early recurrent events.

Early treatment with heparin (< 6 hours) was an independent factor for a better functional outcome in the study. This time point was used because it represents the most frequent time delay selected in current clinical trials evaluating the benefits of new acute stroke therapies. Although we did not randomize the time to initiation of treatment, the absence of significant differences in baseline stroke severity or radiological findings observed between both groups (patients treated within 6 hours vs patients treated after 6 hours) suggested that the results obtained in functional outcome were not fortuitous. Further, multivariate analysis was performed to control for the potential effects of confounders.

Recent advances in our understanding of the biological effects of heparin have shown that besides its antithrombotic effects heparin also has anti-inflammatory properties, including the suppression of the complement system, blockage of neutrophil accumulation, and inhibition of several cytokines. In agreement with these anti-inflammatory properties, the role of heparin is currently being evaluated in such conditions as Crohn disease and ulcerative colitis. Recently, Yanaka et al. found, in a rat model of transient ischemia, that heparin significantly inhibited leukocyte accumulation by antagonizing the function of cell adhesion molecules in ischemic tissue, reduced the size of the infarction, and improved neurological outcome. A body of evidence also indicates that cytokines play an important role very early after focal occlusions of cerebral arteries and that this reaction depends in part on the ability of these agents to block selectins on leukocytes and platelets and on the leukocyte integrin Mac-1 (CD11b/CD18). Therefore, heparin could interfere in cell adhesive interactions between leukocytes and endothelial cells. As expression of cell adhesion molecules reaches maximum levels 6 hours after activation, it can be speculated that patients who received heparin within 6 hours from the onset of symptoms obtained a greater clinical benefit by an earlier modulation of these inflammatory pathways. Regardless of the basic mechanisms at play, our encouraging observations suggest that the role of heparin in acute stroke with NVAF should be assessed in a larger prospective study of patients with symptoms lasting for less than 6 hours, in agreement with clinical trials currently evaluating the role of neuroprotective drugs.

In summary, our findings indicate that neither pretreatment stroke severity nor individual patient traits should delay anticoagulation in alert patients with stroke and NVAF if close APTT monitoring is instituted to prevent both excessive anticoagulation, with its risks of hemorrhage, and inadequate anticoagulation, with its attendant risk of recurrent embolic complications. The better outcome observed in those patients who underwent anticoagulation within 6 hours is encouraging and suggests a neuroprotective mechanism of heparin. Whereas the classic approach to the value of heparin therapy in acute stroke has mainly considered the risks of hemorrhagic complications and early recurrence, our data argue that the therapeutic decision should also contemplate the odds of clinical recovery depending on the delay to treatment initiation. Based on these findings, we recommend a new prospective trial designed under the “time-is-brain” rule to confirm (or deny) the value of early anticoagulation in acute stroke with NVAF.

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Reprints: Angel Chamorro, MD, Neurology Service, IDIBAPS, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.

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