Venous thromboembolism in patients with intracranial haemorrhage

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Dear Sirs,

Current guidelines from the American College of Chest Physicians (ACCP) recommend that patients with acute venous thromboembolism (VTE) be treated initially with low-molecular-weight heparin (LMWH), unfractionated heparin or fondaparinux, followed by long-term treatment with vitamin K antagonists (1). However, there is uncertainty about the optimal therapy in patients with recent intracranial haemorrhage, since they are often excluded from randomised clinical trials of anticoagulant therapy. These patients present a particularly difficult therapeutic dilemma because they are perceived to be at substantial risk of re-bleeding if therapy with anticoagulants is prescribed, and of recurrent pulmonary embolism (PE) in the absence of treatment.

RIETE is an ongoing, prospective registry of consecutive patients with symptomatic, objectively proven, acute VTE (2–4). We assessed the three-month outcome of all patients developing VTE less than 30 days after intracranial haemorrhage in RIETE. Intracranial haemorrhage was diagnosed if the patient had an appropriate clinical event, and had a brain CT or MRI that showed a compatible high-density lesion.

Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. During follow-up special attention was paid to any signs or symptoms suggesting recurrent VTE or bleeding complications. Each episode of clinically suspected recurrent VTE required documentation by objective tests. The causes of death were assigned by the attending physicians. Fatal PE, in the absence of autopsy, was defined as any death appearing <7 days after PE diagnosis, in the absence of an alternative cause of death. Fatal bleeding was defined as any death occurring <7 days after a major bleeding episode. Bleeding complications were classified as 'major' if they were overt and required a transfusion of 2 units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal.

Mann-Whitney test and Student's t-test were used to compare continuous variables. Categorical variables were compared by the Fisher exact test, and the odds ratios and corresponding 95% confidence intervals were calculated. Survival curves were constructed according to the Kaplan-Meyer method. SPSS software (version 15, SPSS Inc. Chicago, IL, USA) was used for statistical management of the data.

Of 27,029 VTE patients enrolled from March 2001 to August 2009, 141 (0.5%) had the VTE <30 days after intracranial haemorrhage (elapsed time: median 17 days, interquartile range 10–23). Of these, 66 patients (47%) had spontaneous intracerebral haemorrhage, 34 (24%) bled after trauma, 15 (11%) had subarachnoidal haemorrhage, 11 (7.8%) neurosurgery, six (4.3%) subdural haematoma, three (2.1%) cancer, and six (4.1%) bled after anticoagulant or thrombolytic therapy. Thirty-two patients (23%) had received pharmacologic prophylaxis after intracranial haemorrhage. In all, 70 patients (50%) were diagnosed with PE, and 71 with deep-vein thrombosis (DVT) alone.

Most patients (82%) were initially treated with LMWH (▶Table 1). Three patients (2.1%) did not receive initial therapy with anticoagulants, and 29% underwent insertion of an inferior vena cava filter (elapsed time from VTE diagnosis to filter insertion: median 1 day; interquartile range 0–5 days; range 0–19 days). Then, most patients (67%) received long-term therapy with LMWH. During the three-month follow-up study, seven patients died of PE (initial PE episode 4, recurrent PE 3). Two of them were not receiving anticoagulant therapy: one died during the first few hours after PE diagnosis, with no time to start any therapy; one had a metastatic carcinoma. Seven further patients were receiving LMWH at doses <150 IU/kg/day. Interestingly, all seven patients with fatal PE died during the first week after VTE diagnosis (▶Fig. 1). Additionally, three patients developed major bleeding complications (of whom two had cerebral re-bleeding), and five patients had recurrent DVT. All bleeding events and DVT recurrences appeared beyond the first week.

Treatment decisions in patients with intracranial haemorrhage who subsequently develop VTE are currently made on an empirical individual basis and entail evaluating their expected morbidity and mortality associated with different treatment options. The findings in the current manuscript reveal that many of these patients receive initial therapy at lower than recommended doses of heparin. In our series, one in every 10 such patients died, half of them because of PE, and no patient died of bleeding. Interestingly, all fatal PEs occurred during the first week, thus suggesting that the intensity of anticoagulant therapy (at least during the first week) should be

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higher. Alternatively, a vena cava filter might be inserted.

After the first week of therapy, there were no more fatal PEs, and the incidence of major bleeding outweighed that of recurrent PE. This finding suggests that, during this later phase of treatment, a less aggressive anticoagulant strategy might reduce bleeding events more than it would increase fatal PE. Our 1.4% incidence of intracranial re-bleeding while on anticoagulant therapy may seem unexpectedly low, but most patients received lower than recommended doses of heparin. In a systematic review of 10 prospective studies in 1,880 patients with haemorrhagic stroke, the annual rate of re-bleeding was 2.3% (5). Two studies provided data on recurrence rates in the first three months, and found a 0.5% recurrence rate in non-anticoagulated patients. In those taking anticoagulants the risk may be two- to 10-fold higher (6, 7).

Unfortunately, the lack of neurological data in RIETE limits the quality of this study. It would be interesting to know if bleeding occurred in a typical or atypical site; if predisposing factors were identified; how many patients underwent a new CT scan of the brain after anticoagulant treatment was started and the proportion of those with haematoma enlargement; if there were any changes in the neurological

Table 1: Clinical characteristics, treatment strategies and 90-day outcome of 141 patients with VTE after intracranial haemorrhage, according to their initial presentation.

	PE	DVT alone	P-value
Patients, N	70	71	
Clinical characteristics			
Gender (males)	31 (44%)	46 (65%)	0.018
Age (mean years, IQR)	71 (61–77)	71 (55–76)	0.220
Body weight (mean kg, IQR)	72 (63–80)	70 (64–78)	0.563
Underlying diseases			
Cancer	4 (5.7%)	8 (11%)	0.370
Prior VTE	4 (5.7%)	2 (2.8%)	0.440
Chronic lung disease	4 (5.7%)	5 (7.1%)	0.763
Chronic heart disease	1 (1.4%)	5 (7.1%)	0.209
CrCl levels <30 ml/min	6 (8.6%)	3 (4.2%)	0.326
Initial therapy			
Low-molecular-weight heparin	54 (77%)	62 (87%)	0.218
LMWH dose, IU/kg/day (mean, IQR)	139 (80–194)	128 (60–173)	0.161
Unfractionated heparin	9 (13%)	5 (7.1%)	0.275
Inferior vena cava filter	23 (33%)	18 (25%)	0.358
Long-term therapy			
Vitamin K antagonists	20 (32%)	10 (16%)	0.041
Low-molecular-weight heparin	42 (67%)	53 (75%)	0.074
LMWH dose, IU/kg/day (mean, IQR)	108 (76–173)	110 (64–158)	0.353
90-day outcome			
Major re-bleeding	2 (2.9%)	1 (1.4%)	0.620
Cerebral re-bleeding	2 (2.9%)	0	0.245
Fatal bleeding	0	0	-
Recurrent DVT	3 (4.3%)	2 (2.8%)	0.681
Recurrent PE	0	4 (5.6%)*	0.120
Fatal PE	4 (5.7%)	3 (4.2%)	0.719
Overall death	7 (10%)	7 (10%)	0.978

*Three of these 4 patients died of the recurrent PE. VTE, venous thromboembolism; IQR, inter-quartile range; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; DVT, deep venous thrombosis; PE, pulmonary embolism.

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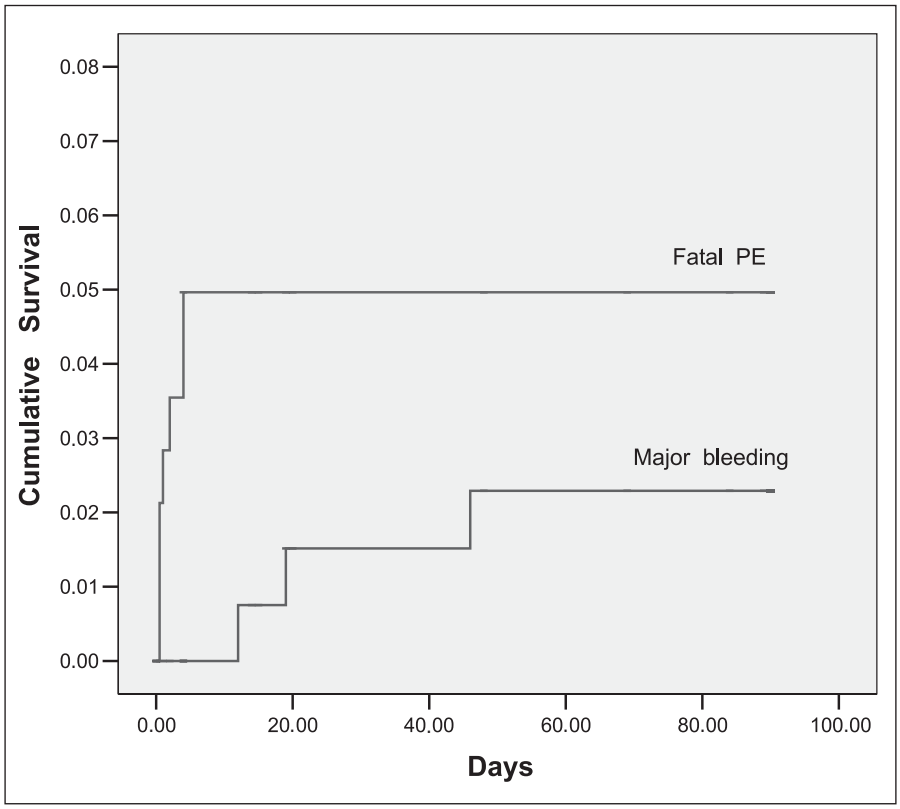

Figure 1: Cumulative incidence of fatal pulmonary embolism and major bleeding in 141 patients with intracranial haemorrhage who subsequently developed venous thromboembolism. PE, pulmonary embolism.

function; how many patients received prohaemostatic agents at the time of intracranial haemorrhage; and how many received pharmacologic thromboprophylaxis before their index VTE event.

In summary, the clinical impact of VTE in patients with intracranial haemorrhage is considerable, since one in every 10 such patients died during the first three months. During the first week after detecting VTE, the main threat is fatal PE; beyond the first week the main threat is bleeding. However, randomised trials would be necessary to verify the benefits of the different therapeutic options in this population.

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Conflict of interest

None declared.

References

1. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133: 454S-545S.
2. Nieto JA, Bruscas MJ, Ruiz-Ribó D, et al. Acute venous thromboembolism in patients with recent major bleeding. The influence of the site of bleeding and the time elapsed on outcome. J Thromb Haemost 2006; 4: 2367–2373.
3. Ruíz-Giménez N, Suárez C, González R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost 2008; 100: 26–31.
4. Vasco B, Villalba JC, Lopez-Jimenez L, et al. Venous thromboembolism in nonagenarians. Findings from the RIETE Registry. Thromb Haemost 2009; 101: 1112–1118.
5. Bailey RD, Hart RG, Benavente O, et al. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracerebral hemorrhage. Neurology 2001; 56: 773–777.
6. Vermeer SE, Algra A, Franke CL, et al. Long-term prognosis after recovery from primary intracerebral haemorrhage. Neurology 2002; 59: 205–209.
7. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. Stroke 1995; 26: 1471–1477.