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High intensity of oral anticoagulant therapy in patients with cerebral haemorrhage: cause or consequence of the bleeding?

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Summary. In assessing the optimal intensity of anticoagulant therapy, the International Normalized Ratio (INR) at admission is used as a basis for INR-specific incidence rates. In 47 patients suffering a haemorrhagic stroke we tested the assumption that the INR at admission is an acceptable measure for the INR that preceded the haemorrhage. We found high D-dimer levels in 70% of the patients, which indicated activated coagulation and fibrinolysis. This was not of such an extent that it could also be measured with other

routine coagulation tests, with the possible exception of two patients. We found normal INRs in 33 non-anticoagulated patients, and only a mildly prolonged INR of 1.9 in one patient, which was most probably caused by a vitamin K deficiency. We concluded that the INR at admission can be used in studies to assess the optimal level of anticoagulation.

Keywords: oral anticoagulant therapy, cerebral bleeding, consumption coagulopathy, INR, optimal intensity.

Oral anticoagulant therapy is effective in the prevention of thromboembolism. An important adverse effect is the increased risk of cerebral bleeding. We developed a method to study the optimal intensity of anticoagulant therapy, i.e. the intensity (expressed in International Normalized Ratio, INR) at which both thromboembolism and bleeding are minimal (Rosendaal *et al*, 1993). With this method, intensity-specific incidence rates of all adverse events are calculated as the ratio of the total number of events which take place at a certain level of anticoagulation and the number of patient-years that this level was achieved by the total patient population. This method has been successfully applied in a number of studies (Azar *et al*, 1996; EAFT study group, 1995; Cannegieter *et al*, 1995; van der Meer *et al*, 1993). These results are all based on the assumption that the INR measured at admission – often several hours after the symptoms started – corresponds to the INR just before the event and is not a consequence of the bleeding.

Several papers have reported coagulation disorders after head injury which in some cases resulted in severe disseminated intravascular coagulation (DIC) (Sande *et al*,

1978; Touho *et al*, 1986). This may be explained by the release of tissue factor from damaged brain tissue into the circulation, which will activate coagulation and secondary fibrinolysis. In patients suffering a stroke, the same mechanism, though less prominent, may be involved in the progression of the stroke. In a number of studies low-grade DIC has been described in stroke patients (Lane *et al*, 1983; van Wersh & Franke, 1993; Landi *et al*, 1987). Especially in anticoagulated patients, a slight activation of coagulation may cause further consumption of the vitamin K dependent clotting factors which are already present in a low concentration. This can result in a higher INR at admission than at the start of the symptoms. If this is the case, the INR at admission is not a reliable measure on which to base INR-specific incidence rates, which implies that the results of studies that use this method are invalid. Therefore we studied the assumption that the INR at admission is an acceptable measure for the INR that preceded the haemorrhage.

METHODS

Forty-seven consecutive patients with an intracranial bleed and who were hospitalized within 24 h of the onset of symptoms took part in the study. Patients were excluded if no computer tomography scan of the brain was performed or no blood sample was obtained before any therapy was given. In

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Table I. Results of coagulation and fibrinolysis markers.

Tests	Oral anticoagulant treatment		Reference ranges
	Yes (n = 13) mean (range)	No (n = 34) mean (range)	
Platelets ($\times 10^9/l$)	237 (164–333)	245 (147–387)	150–400
APTT (s)	38.3 (27.9–46.7)	25.1 (19.4–35.9) ¹	25.0–33.0
PT (s)	33.4 (23.9–42.5)	11.7 (10.1–19.6) ²	11.5–14.5
INR	3.8 (2.5–5.1)	1.0 (0.8–1.9) ²	0.9–1.3
FVIII:c (IU/ml)	2.28 (1.37–3.12)	1.92 (0.39–3.06) ³	0.65–1.35
FV (%)	104 (84–130)	113 (74–162)	0.75–125
Fibrinogen (g/l)	4.7 (2.8–8.6)	3.1 (1.7–5.3)	1.7–4.5
D-dimer (ng/ml)	312 (29–1022) ⁴	295 (21–1978) ⁵	0–80

¹ Three patients exceeded the upper limit of the reference range.

² One patient exceeded the upper limit of the reference range.

³ One patient had a FVIII:c under the lower limit.

⁴ Nine patients exceeded the upper limit of the reference range.

⁵ 23 patients exceeded the upper limit of the reference range.

addition to patients with oral anticoagulant therapy, we also included patients without this treatment to compare the extent of the activation of the coagulation.

Activated partial thromboplastin time was measured with Cephotest (Nycomed, Oslo, Norway), prothrombin time with Thromborel S (Behringwerke AG, Marburg, Germany), and was also expressed as INR (International Normalized Ratio). Fibrinogen concentration was derived from the prothrombin time. Fibrinogen degradation products were measured with TintElize® D-dimer (Biopool, Umea, Sweden). Factor VIII coagulant activity (FVIII:c) was measured with Automated APTT (Organon Teknika, Durham, U.S.A.) and FVIII-deficient plasma. Factor V coagulant activity was measured with Thromborel S (Behringwerke AG, Marburg, Germany) and FV-deficient plasma. Platelets were counted with a Coulter counter. Laboratory reference values were obtained from 78 healthy volunteers, age range 20–60 years.

To study whether differences in coagulation parameters might depend on the type of bleeding, we classified the bleed as subdural, subarachnoidal or intracerebral. For the same reason, we categorized the severity of the haemorrhage as: (1) fatal within 30 d; (2) residual effects; (3) full recovery.

RESULTS

Table I shows the results of the haemostatic tests in the 47 patients. 13 patients received anticoagulant therapy for various reasons. In four patients the INR was not in the therapeutic range at admission: in two it was above, and in two it was below the normal range. The APTT was prolonged in most anticoagulated patients. The values of the other coagulation tests were normal, with the exception of the D-dimer assay.

In the 34 non-anticoagulated patients, all values of the platelet count, factor V activity and fibrinogen were in the normal ranges. In three patients the APTT was marginally prolonged (34.0–35.9 s), and in one of these patients the PT

was also mildly prolonged (19.6 s). This last patient also had an elevated INR (1.9). In another patient (APTT 34.0 s, normal PT), factor VIII:c was low at 0.39 IU/ml.

FVIII:c was high in the majority of the patients (72% had activity > 1.70 IU/ml) and was found in both the anticoagulated and the non-anticoagulated groups. High D-dimer levels were found (> 80 ng/ml) in 32 patients (68%). This percentage was the same for patients with and without anticoagulant treatment.

Table II summarizes the clinical results. All events but one had occurred spontaneously. Mortality was higher for patients on anticoagulant treatment: 60% died, compared to 29% of the patients without anticoagulant treatment. No

Table II. Patient characteristics.

	Oral anticoagulant treatment	
	Yes (n = 13) n (%)	No (n = 34) n (%)
Age (years)		
< 50	0 (0)	8 (24)
50–69	5 (38)	16 (47)
≥ 70	8 (62)	10 (29)
Sex		
Men	8 (62)	19 (56)
Women	5 (38)	14 (41)
Type		
Subarachnoidal	1 (8)	7 (21)
Intracerebral	11 (85)	26 (76)
Subdural	1 (8)	0 (0)
Severity		
Fatal	10 (60)	10 (29)
Residual effects	2 (15)	21 (62)
Full recovery	0 (0)	3 (9)

differences in haemostatic tests could be demonstrated between patients with a fatal or a non-fatal bleeding, with the exception of D-dimer levels. In eight patients very high D-dimer levels were found (> 500 ng/ml), whereas all other factors were within the normal range. Seven of these patients died as a result of the bleeding. The three types of haemorrhage differed also in D-dimer levels only: mean D-dimer in patients with subarachnoidal bleeding was 638 ng/ml whereas in patients with intracerebral bleeding this was 219 ng/ml.

DISCUSSION

Normal routine coagulation tests were found in the majority of 47 consecutive patients with intracranial bleeding. Three non-anticoagulated patients had a slightly prolonged APTT. In the first of these three the PT was also slightly prolonged although all other parameters were normal. Since coumarin therapy was denied at admission, the most probable explanation is vitamin K deficiency. A consumption coagulopathy is unlikely since all other parameters were normal, including D-dimer. A second patient, a young man aged 36 years, had a low FVIII:c of 0.39 IU/ml which explained his slightly prolonged APTT. Several months later his FVIII:c was normal. Even though all other parameters were normal at admission, coagulation activation may be likely. In the third patient no other abnormalities were found, with the exception of elevated D-dimer levels. So, in this case it may also be concluded that the prolonged APTT was caused by a mild consumption coagulopathy.

A remarkable finding was the high levels of FVIII:c in most patients. Almaani *et al* (1987) found an association between high FVIII:Ag and mortality in 42 patients with intracranial haemorrhage. Landi *et al* (1987) also reported higher FVIII:c in stroke patients who died than in survivors. We did not find an association with mortality nor with abnormalities in the other coagulation parameters.

We found high D-dimer levels in about 70% of the patients. Van Wersch & Franke (1993) also found elevated D-dimer levels in 27/34 patients with cerebral haemorrhage. The high D-dimer levels indicate activated coagulation and fibrinolysis in patients with a cerebral haemorrhage, which is not of such an extent that it can also be measured with other routine coagulation tests, such as in DIC. In this series of 47 patients this was possibly the case in two patients only; however, this did not affect the INR. We found normal INRs in 33 non-anticoagulated patients, and only a mildly

prolonged INR of 1.9 in one patient, which was most likely brought about by vitamin K deficiency.

The aim of this study was to test the assumption that the INR at admission is an adequate measure for the INR at the start of the bleeding and not a result of the bleeding. We conclude that this is a valid assumption and that the INR at admission can therefore be used in studies to assess the optimal level of anticoagulation.

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