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Managing the therapeutic dilemma: patients with spontaneous intracerebral hemorrhage and urgent need for anticoagulation

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Abstract Physicians face a therapeutic dilemma in patients with acute hemorrhagic stroke requiring long-term, high-intensity anticoagulants because this treatment increases the risk of intracranial hemorrhage (ICH) 8- to 11-fold. We retrospectively studied 15 patients with ICH which occurred under anticoagulation with phenprocoumon, with an international normalized ratio (INR) of 2.5–6.5 on admission. Hemispheric, thalamic, cerebellar, intraventricular, or subarachnoid hemorrhage without aneurysm occurred. Absolute indications for anticoagulation were double, mitral, or aortic valve replacement, combined mitral valve failure with atrial fibrillation and atrial enlargement, internal carotid artery-jugular vein graft, frequently recurring deep vein thrombosis with risk of pulmonary embolism, and severe nontreatable ischemic heart disease. As soon as the diagnosis of ICH was established, INR normalization was attempted in all patients by administration of prothrombin complex, fresh frozen plasma, or vitamin K. After giving phenprocoumon antagonists (and neurosurgical therapy in four patients) heparin administration was started. Nine patients received full-dose intravenous and six low-dose subcutaneous heparin. The following observations were made: (a) All patients with effective, full-dose heparin treatment with a 1.5- to 2-fold elevation in partial thromboplastin time after normalization of the INR were discharged without complication. (b) Three of four of the patients with only incomplete correction of the INR (> 1.35) experienced relevant rebleeding within 3 days (all patients with an INR higher than 1.5), two of whom were on full-dose heparin. (c) Three of seven of the patients with normalized INR and without significant PTT elevation developed severe cerebral embolism. Although our data are based on a retrospective analysis, they support treatment with intravenous heparin (partial thromboplastin time 1.5–2 times baseline value) after normalization of the INR in patients with an ICH and an urgent need for anticoagulation.

Key words Anticoagulation · Intracerebral hemorrhage · Prosthetic valve cerebral ischemia · Treatment

Introduction

Long-term, high-intensity, oral anticoagulant therapy increases the risk of intracranial hemorrhage (ICH) 8- to 11-fold [1], corresponding to a statistical incidence of 1% per patient-year [2, 3]. The frequency of anticoagulant-related ICH is not correlated with the duration of therapy [4] or with prothrombin time or thrombotest values [5, 6]. Bleeding severity, however, is increased with lower prothrombin time values, particularly those below 20% as measured by the Quick one-stage method [7, 8].

An obvious therapeutic dilemma arises when a patient who requires high-intensity anticoagulation for high risk of thromboembolism is admitted with acute spontaneous ICH. Fatal thromboembolism may be expected after tapering high-intensity coagulation, particularly in patients with heart valve prostheses or with atrial fibrillation accompanied by severe heart failure, vitium cordis, or previous embolism. All patients with mechanical prostheses, regardless of the design or site of placement [9], are at risk of thromboembolism. Mitral heart valve prostheses carry a risk of embolism that is almost twice as high as aortic valve prostheses [2]. Without efficient anticoagulation the incidence of thromboembolism is 3- to 6-fold higher than with conventional doses [10]. The frequency of symptomatic embolism within 8 years is reported to be as high as 11% [11]. Cannegieter et al. [2] found an incidence of major embolism of 4 per 100 patient-years. A risk of embolism is even present in patients receiving oral anticoagulation [9], with an incidence of 1–2 nonfatal and 0.2 fatal events per 100 patient-years; Cannegieter et al. [3] report an incidence of cerebral embolism of 0.7 per 100 patient-years.

On the other hand, continuing of anticoagulation treatment in order to prevent these disabling and life-threatening complications may increase the risk of clot expansion or rebleeding. The rather favorable outcome in patients with, for instance, small anticoagulation-associated ICH may be worsened, and life-threatening rebleedings with mass effect may follow. Reports addressing issues such as the duration of discontinuation, the time to resume anticoagulant therapy after ICH, or the assessment of the risk of rebleeding when treatment is continued, and the type of anticoagulation are rare and their findings controversial [4, 12–18]. Previous studies and case series concerning the therapeutic dilemma in patients with spontaneous ICH and need for anticoagulation are the following: Kawamata et al. [4] (n = 27), Babikian et al. [12] (n = 6), Gomez et al. [13] (n = 1), Nagano et al. [14] (n = 4), Lieberman et al. [15] (n = 6), Nagakawa et al. [16] (n = 4), Wijdick et al. [17] (n = 39), and Leker and Abramsky [18] (n = 4). Thus from our study the literature, no confident recommendation can be made for optimal management that comprises minimal risk of secondary neurovascular complications.

Our study of the acute management of patients with ICH and an urgent need for anticoagulation compared the risk and the benefit of various treatment strategies and effects, such as (a) full-dose heparin after rapid normalization of the international normalized ratio (INR), (b) incomplete correction of the INR, and (c) rapid normalization of INR combined with low-dose heparin for prophylaxis of deep venous thrombosis.

Patients and methods

Patient characteristics

We retrospectively analyzed the cases of patients admitted to the Neurological and Neurosurgical Departments of the University of Heidelberg between 1992 and 1997 who received oral anticoagulation treatment, and who had ICH as documented by computed tomography (CT). We excluded patients with a weak indication for anticoagulation and those with endocarditis or metastatic cancer. Three men were also excluded secondarily because crucial laboratory data were available; two of them were admitted with a major bleeding and signs of herniation and died 2–3 days later, and one received prothrombin complex (prothrombin, proconvertin, Stuart-

Table 1 The baseline clinical characteristics [*MVR* prosthetic mitral valve replacement, *AVR* prosthetic aortic valve replacement, *AF* atrial fibrillation, *IHD* ischemic heart disease, *MF* mitral valve failure, *DVT* deep vein thrombosis, *INR* international normalized ratio, *PT* prothrombin time (Quick one-stage method), *PTT* partial thromboplastin time, *PLT* thrombocyte count, *n.a.* not available]

Patient no.	Age (years)	Sex	Site of hemorrhage	Indication for phenprocoumon	Coagulation on admission		
					INR (PT)	PTT	PLT
1	57	F	Cerebellar	MVR	2.92 (19%)	27	180
2	67	M	Thalamic	MVR	3.88 (14%)	45	261
3	65	M	Temporal-parietal	AVR + MVR + AF	2.92 (19%)	44	161
4	62	M	Subarchnoid (without aneurysm)	AVR	5.05 (14%)	52	276
5	61	M	Thalamic	AVR	3.23 (17%)	48	280
6	70	F	Subarchnoid (without aneurysm)	MVR + AF	6.49 (< 10%)	48	432
7	70	F	Cerebellar	AVR	5.65 (< 10%)	42	281
8	53	M	Hemispheric	AVR	3.23 (17%)	61	156
9	60	M	Temporal	MVR + AF	2.52 (21%)	38	282
10	46	M	Hemispheric	MVR	2.39 (24%)	41	962
11	65	M	Frontoparietal	Severe IHD, renal artery stents	6.11 (< 10%)	n.a.	n.a.
12	51	M	Occiptial	ACI-IJV graft	6.11 (< 10%)	66	314
13	68	M	Intraventricular	MI + AF	7.92 (< 10%)	n.a.	n.a.
14	65	F	Parieto-occipital	Comb. MF + AF	3.07 (18%)	120	n.a.
15	60	F	Thalamic	Frequently recurrent DVT	2.79 (20%)	37	306

Prower factor, and antihemophilic globulin) and died a few hours later.

The series included 15 patients (5 women, 10 men; aged 46–70 years, median 62). Details of clinical, laboratory, and CT findings upon admission and during in-hospital treatment were taken from the medical records. Baseline clinical characteristics are presented in Table 1. Seven patients presented with hemispheric or lobar hemorrhages, three with thalamic, two with cerebellar, two with subarachnoid hemorrhage without aneurysm, and one with intraventricular hemorrhage.

The indication for high-intensity anticoagulation was double valve replacement with atrial fibrillation in one patient, prosthetic mitral valve replacement in five (two of them also suffering from atrial fibrillation), prosthetic aortic valve replacement in four, combined mitral valve failure with atrial fibrillation and atrial enlargement in two, and internal carotid artery-jugular vein graft, frequently recurring deep vein thrombosis with risk of pulmonary embolism, and severe nontreatable ischemic heart disease, and designation for heart transplantation in one patient each. Every patient received oral anticoagulation treatment with phenprocoumon, with an INR of 2.5–6.5 on admission. No patient had used any nonsteroidal antiphlogistic drug during the weeks before admission. Their platelet counts were normal.

Acute treatment

As soon as the diagnosis of ICH was established, anticoagulation was reversed and INR normalization attempted in all patients. They received prothrombin complex (prothrombin, proconvertin, Stuart-Prower factor, antihemophilic globulin B), fresh frozen plasma, intravenous phytomenadione (vitamin K), or a combination thereof. After INR normalization and neurosurgical therapy (in four patients), heparin treatment was started (11 patients on day 1, two patients on day 2, two patients on day 3); nine patients received full-dose intravenous and six patients low-dose subcutaneous heparin.

Outcome assessment

The following factors were assessed to determine the risk or benefit of various treatment strategies: age; site of hemorrhage; underlying disease indicating oral anticoagulation; relevant laboratory findings, including the INR, prothrombin time, partial thromboplastin time (PTT), and thrombocyte count upon admission and at endpoint; and the therapeutic regimen and its effectiveness at the endpoint. We defined the following events as the endpoints of this study: (a) discharge to another hospital or rehabilitation unit without any secondary neurovascular complication, (b) evidence of a rebleeding on follow-up CT after clinical deterioration, (c) evidence of thromboembolism on follow-up CT after clinical deterioration.

Results

Outcome

Acute treatment and outcome of each patient are summarized in Table 2. Of the 15 patients 9 (60%) were transferred without any cerebrovascular complications as established by CT or clinically. Three patients showed clinical deterioration within 3 days, and CT revealed significant rebleeding (20%, e.g., Fig. 1). One of these patients died 4 days later due to the developing mass effect (case 15). Three patients (20%) experienced major thromboembolic events with extended infarction of the middle, the posterior or bilateral anterior cerebral artery territory within 4 days.

Table 2 Early treatment with emphasis on coagulation management and results as documented by CT and clinical status. (*parentheses* ineffective treatment, *PPSB* prothrombin complex, *FFP* fresh frozen plasma, *OP* surgical treatment, *ACM* middle cerebral artery, *ACP* posterior cerebral artery, *ACA* anterior cerebral artery, *CPR* cardiopulmonary resuscitation, *ICH* intracranial hemorrhage)

Patient no.	Initial therapy (day of heparin initiation)	Result	Day of treatment	Coagulation at endpoint		
				INR (PT)	PTT	PLT
1	PPSB, phytomenadione, low-dose heparin (1)	Large ACM infarction	5	1.13 (81%)	23	191
2	PPSB, phytomenadione, full-dose heparin (1)	Discharge without complication	3	1.23 (66%)	31	n.a.
3	PPSB, phytomenadione, heparin (1) withdrawal for OP	Large ACM infarction	4	1.10 (88%)	27	127
4	PPSB, phytomenadione, full-dose heparin (1)	Discharge without complication	7	1.06 (81%)	50	285
5	PPSB, phytomenadione, full-dose heparin (1)	Discharge without complication	16	1.21 (69%)	58	204
6	FFP, phytomenadione, full-dose heparin (2)	Discharge without complication	3	1.15 (73%)	26	334
7	(PPSB, phytomenadione), full-dose heparin (1)	Rebleeding	3	1.48 (46%)	57	245
8	(PPSB, FFP) OP, full-dose heparin (1)	Rebleeding	3	3.23 (17%)	62	178
9	Phytomenadione, i.v., full-dose heparin (3)	Discharge without complication	8	1.2 (87%)	68	187
10	PPSB, OP, full-dose heparin (2)	Discharge without complication	8	1.01 (111%)	50	730
11	FFP, PPSB, low-dose heparin (1)	Discharge without complication	4	1.11 (85%)	29	246
12	PPSB, phytomenadione, OP, full-dose heparin (1)	CPR (unknown reason), no ICH, no CI	8	1.08 (91%)	38	263
13	PPSB, low-dose heparin (1)	Discharge without complication	19	1.35 (55%)	28	n.a.
14	PPSB, low-dose heparin (1)	ACP and bilateral ACA infarctions	2	0.91 (115%)	38	266
15	(FFP, phytomenadione), low-dose heparin (3)	Rebleeding	2	1.91 (32%)	41	252

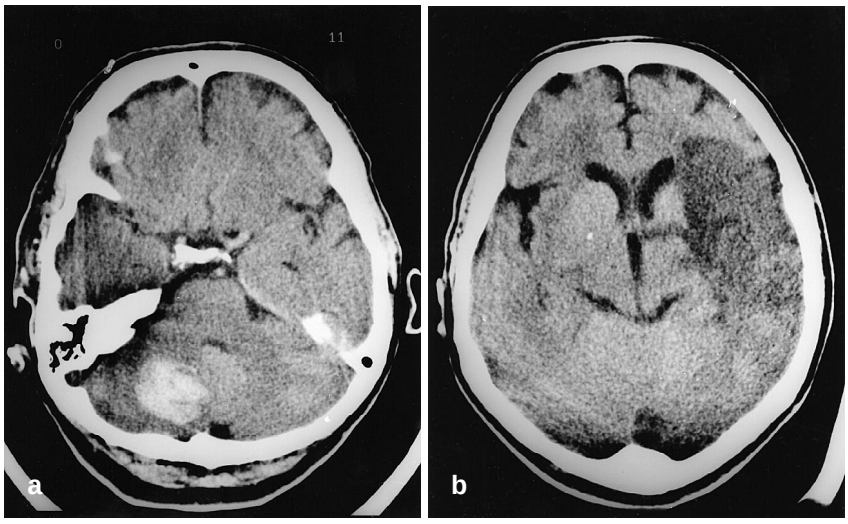

Fig. 1 **a** CT of patient 1 (Tables 1, 2) on admission showed left hemispheric cerebellar hemorrhage. **b** Follow-up CT after normalization and administration of low-dose heparin revealed a large infarction in the left middle cerebral artery territory on day 4 due to distal embolic carotid artery occlusion as shown by angiography

Table 3 Endpoint coagulation status during acute management, independent of the therapeutic goal

	INR normal				INR increased				Total	
	PTT increased		PTT normal		PTT increased		PPT normal		*n*	%
	n	%	*n*	%	*n*	%	*n*	%		
No secondary cerebrovascluar complication	4	27	4	27	0	–	1	7	9	60
Rebleeding	0	–	0	–	2	13	1	7	3	20
Symptomatic cerebral embolism	0	–	3	20	2	–	0	–	3	20
Total	4	27	7	47	2	13	2	13	15	100

Coagulation status at different endpoints

We evaluated the coagulation status at endpoint (Table 3). All three patients with rebleedings or expansion of hemorrhage showed an increase in INR by more than 1.5, with an additional increase in PTT in two patients. The unintended INR increase occurred secondarily after INR normalization had already been achieved after admission. Each of the three patients suffering from major cerebral embolic complications showed both effectively normalized INR and normal PTT, due either to the low-dose heparin therapy (two patients) or to heparin withdrawal for surgical intervention (one patient). Two patients had mitral valve replacement, and one patient had combined mitral valve failure with atrial fibrillation and enlargement.

A normalized INR was achieved in eight of the nine patients without any secondary cerebrovascular event. In one patient this had increased again to 1.35 at endpoint. Seven were treated with full-dose intravenous heparin, leading to a constant PTT increase in four and an inconsistently effective increase in three patients (in three ineffective at endpoint). Two patients had received low-dose heparin.

With regard to coagulation treatment and status, the following observations were made: (a) Effective full-dose heparin treatment with a 1.5- to 2-fold PTT elevation was associated with discharge without complications in all four patients. (b) Three of the four of the patients in whom correction of the INR was unsuccessful due to a secondary increase (1.35–3.2) experienced rebleeding within 3 days (each with an INR higher than 1.5). (c) Three of the seven of patients with normalized INR and without significant PTT elevation due to low-dose or temporarily ineffective full-dose heparin administration developed severe cerebral embolism

Discussion

We report a series of patients who urgently needed anticoagulation treatment, which, however, was complicated by ICH. This obvious therapeutic dilemma is increasingly common because more patients are receiving warfarin for prosthetic heart valves (PHV) or other medical or neurological indications. Therefore it is important to develop a therapeutic regimen which comprises both a minimal risk of rebleeding and thrombembolic events.

Interestingly, all patients in our study who received full-dose heparin to prevent thromboembolism after normalization of the INR were discharged without rebleed-

ing. This is in accordance with other reports. A recently published study reported four patients with ICH and PHV who received full-dose heparin and who experience a PTT increase of 1.5–2 times baseline. Heparin was started 24 h after admission in three patients and 36 h after surgery in one [14]. None of the patients experienced rebleeding or embolic events. In the series of Kawamata et al. [4] anticoagulation treatment was resumed in 12 patients with ICH and PHV within 3 days without any complications due to rebleeding. Nagakawa et al. [16] report four patients, three of whom received heparin at an early stage and survived without any secondary cerebrovascular event. Only Lieberman et al. [15] have reported fatal rebleeding after early resumption of heparin in one patient with ICH and PVR; however, they did not report the coagulation parameters, particularly INR, at the time of rebleeding.

These observations are surprising since heparin therapy is known to increase the risk of cerebral bleeding [19–22]. Heparin helps to inhibit fibrinogen from converting to fibrin and thereby clot formation by binding to antithrombin III [23]. However, this is true for patients who have previously suffered an ischemic stroke, while bleeding complications are uncommon in patients without any known previous cerebrovascular event if heparin is well controlled [24]. Furthermore, two studies have shown anticoagulation therapy with full-dose-heparin to be safe even in patients with embolic hemorrhagic infarction [25, 26]. When given early after the event, heparin neither increases the extension of the hemorrhagic transformation nor alters prognosis. There is some pathophysiological evidence confirming the observation that heparin does not increase the size of cerebral hematoma when coagulation factors returned to normal levels. Pathoanatomical investigations reveal that patients with changes in the small arteries predisposing for ICH, such as hyalinosis, focal angionecrosis, and microaneurysms have small globar hemorrhages [27]. These may evolve to definite mass lesions under anticoagulation treatment. However, once a lesion is present, and the INR is normalized, the anticoagulant effect of heparin may be counteracted by the extrinsic coagulation pathway which is activated locally by the tissue lesion. Brain tissue contains a large quantity of tissue thromboplastin, in particular tissue factor (astrocytes [28]), the major cellular initiator of the coagulation protease cascades of which the fibrinolytic activity is very low [29, 30].

Damage to brain tissue is known to cause the release of tissue thromboplastin, which activates the extrinsic clotting cascade. Therefore under heparin treatment rebleeding may be less likely than new-onset bleeding when this system has not yet been activated. Furthermore, heparin may not be able to enter the site of cerebral hemorrhage in significant doses since the small vessels are compressed within the hematoma.

Our data indicate that patients with ICH and inhibition of the extrinsic coagulation pathway by increased INR to a minimum of 1.5 are at high risk of rebleeding. This is evident in terms of pathophysiology, but, to our knowledge, it has rarely been addressed in the literature. In the series of Kawamata et al. [4] six patients suffered early rebleeding despite withdrawal of warfarin. In these patients INR could be still increased since only intravenous vitamin K was administered as antagonist; in one patient the thrombotest value was 15% at this time. The effectiveness of INR normalization for emergency discontinuation of anticoagulant treatment seems crucial. The use of prothrombin complex promotes INR normalization and improves the prognosis of patients treated after ICH [31].

Even the short-term discontinuation of anticoagulation places patients with mitral valve replacement or combined mitral failure with atrial fibrillation at high risk of cardiac embolization. This observation is consistent with other reports. In the series of Kawamata et al. [4] one of the 20 patients with PHV suffered thromboembolic complications of the brainstem despite early postoperative initiation of heparin treatment within 3 days, indicating that there was thrombus formation or increase during this short interval of anticoagulation withdrawal. In the series of Nagakawa [16] the only patient who did not receive early heparin developed myocardial infarction due to coronary artery embolism 2 days after ICH and died. Gomez et al. [13] reported another patient with PHV and a cerebral embolic event 10 days after discontinuation of heparin following ICH.

However, our observations concerning this point are in contrast with a recently published series of 39 surviving patients with PVH and ICH [18]. None of the surviving 26 patients, including the nine at high risk of embolization experienced any embolism during the discontinuation of anticoagulation treatment for periods of 2 days–3 months. The authors concluded that it is safe to discontinue heparin during the acute hospital treatment within this interval. These results confirm the observation of Lieberman et al. [15], who found that two patients with aortic valve replacement in whom anticoagulants were not resumed did well under antiplatelet therapy. In another series of six patients with ICH and PHV [12] warfarin was discontinued immediately and safely resumed after 8–42 days.

Although our study comprises fewer patients than the sum of patients from these three reports, the clarity of our findings concerning this point indicates that their conclusion that withdrawal of any anticoagulation treatment for more than 1 week is safe cannot be maintained as a guideline in the acute management of patients with ICH and with urgent need for anticoagulation. Furthermore, the authors did not report transesophageal echocardiographic evaluations or clinical follow-up to exclude thrombosis of the prosthesis, which may have become symptomatic after hospital treatment of the acute condition.

The present study is considerably limited by the small number of patients. However, full-dose intravenous heparin treatment must be discussed in patients with ICH

and a high risk of cerebral thromboembolism, provided that early, active, and sustained normalization of the INR over the first week of the acute illness is guaranteed. Full-dose heparin prevents embolic events and does not seem to cause rebleeding or bleeding expansion when INR has been normalized. This must be achieved with prothrombin complex or fresh-frozen plasma administration and careful monitoring of blood coagulation to detect fatal secondary INR increase. However, from our data allow no absolute recommendation for an optimal treatment of these patients. Further, prospective studies are thus required to address these questions.

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