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Thromboprophylaxis and Early Antithrombotic Therapy in Patients with Acute Ischemic Stroke and Cerebral Venous and Sinus Thrombosis

M. Busch and F. Masuhr

Department of Neurology, Charité Medical School, Humboldt University, Berlin, Germany

Abstract: So far, neither treatment with standard unfractionated heparin (UFH) nor with low-molecular-weight heparin (LMWH) has been shown to reduce mortality or to improve neurological outcome in patients with acute ischemic stroke. Although a reduction of early recurrent stroke has been demonstrated for the use of subcutaneous UFH, this benefit was offset by a similar-sized increase in hemorrhagic stroke. Double-blinded studies of LMWH have demonstrated no difference between active treatment and placebo suggesting that LMWH is not effective for the early secondary prevention of ischemic stroke. Although UFH and LMWH may be beneficial in certain subgroups of stroke who are at high risk for early stroke recurrence, these subgroups are still to be defined. Currently, low-dose UFH and LMWH can only be recommended for prophylaxis of deep vein thrombosis in patients with acute ischemic stroke with impaired mobility or other factors determining a particular high risk of venous thromboembolism. Available treatment data from controlled trials favor the use of anticoagulation as the first-line therapy for patients with cerebral venous and sinus thrombosis because it may reduce the risk of a fatal outcome and severe disability and does not promote intracranial hemorrhage.

Key words: ischemic stroke; anticoagulation; cerebral venous thrombosis; outcome

Introduction

Antithrombotic therapy is a crucial part of modern treatment of ischemic stroke, including antiplatelet agents and anticoagulants in acute stroke and in the long-term prevention of stroke recurrence. While oral anticoagulants have an established role in the secondary prevention of cardioembolic stroke, early anticoagulation with heparin in the acute stage of ischemic stroke remains controversial. Potential benefits of early anticoagulant therapy include the improvement of stroke outcome, the reduction of early stroke recurrence and the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in immobilized patients. However, these beneficial effects may be counterbalanced by a substantial increase of severe bleeding complications, particularly intracranial hemorrhage.

Studies in the prevention and therapy of venous thromboembolism (VTE) and in patients with acute coronary syndromes have shown that low-molecular-weight heparins and heparinoids (LMWH) are superior to standard unfractionated heparin (UFH) as they caused less bleeding and other serious adverse events (Cohen et al. 1997, Geerts et al. 2001, Leizorovicz et al. 1992, Lensing et al. 1995). This clinical difference between UFH and LMWH is likely to be a result of differences in their pharmacokinetic features and their mechanisms of action (Bath 1998). LMWH have a higher bioavailability, a longer half-life and a reduced protein binding, thereby producing a more predictable anticoagulant effect and they can safely be administered subcutaneously once or twice daily without monitoring. Moreover, LMWH have less antiplatelet activity than UFH and do not increase vascular permeability which may also contribute to a reduced risk of bleeding. Given these pharmacological advantages over UFH, LMWH may improve safety and efficacy of early anticoagulant therapy in patients with acute ischemic stroke as well. Over the last couple of years, numerous clinical trials have examined the utility of early anticoagulant therapy with UFH or LMWH in acute ischemic stroke. This review presents their results and especially focuses on the published evidence of LMWH use in patients with acute ischemic stroke.

Effect of Early Anticoagulation on Stroke Mortality and Stroke-related Morbidity

So far, neither treatment with standard unfractionated heparin (UFH) nor with low-molecular-weight heparin (LMWH) has been shown to reduce mortality or to improve neurological outcome in patients with acute ischemic stroke. For the use of UFH, the International Stroke Trial (IST) reported a negative result (International Stroke Trial Collaborative Group 1997). This randomized and open trial included almost 20 000 pa-

tients and studied the safety and efficacy of subcutaneous UFH and aspirin within 48 hours of stroke onset in four different treatment groups: (1) aspirin 300 mg daily, (2) heparin at two doses (5000 or 12500 IU twice a day), (3) aspirin plus heparin, and (4) no aspirin and no heparin which were studied in a multifactorial design. Treatment continued for 14 days and the primary outcomes were death within 14 days and death and dependency at 6 months. Heparin (low- and high-dose group combined) treatment was associated with non-significantly fewer deaths within 14 days (9.0% heparin vs. 9.3% no heparin). At 6 months the percentage of patients who were dead or dependent was identical in both groups (62.9%). At the same time, heparin was associated with a significant excess of 9 transfused or fatal extracranial bleeds per 1000 patients treated. Thus, UFH showed no statistically significant benefit on the primary outcomes, hence showing no beneficial effect on the improvement of neurological outcome or a reduction of mortality. Aspirin therapy was also associated with only non-significantly fewer deaths within 14 days (9.0% aspirin vs. 9.4% no aspirin) but at 6 months the number of patients who had died or were dependent was (after adjustment for baseline prognosis) significantly lower in aspirin-allocated patients (14 per 1000 treated patients). Thus, aspirin showed a small but worthwhile improvement at 6 months.

Six major trials of LMWH in acute ischemic stoke have been published (see Table 1 for trial characteristics). One small trial with nadroparine (4100 anti-factor Xa IU twice a day versus 4100 IU daily versus placebo within 48 hours of stroke onset) reported a significant, dose-dependent benefit with a better clinical outcome (death or dependency) 6 months after the stroke in patients receiving the high-dose with no significant increase in the rate of hemorrhagic complications (Kay et al. 1995). However, a larger European study could not confirm this beneficial effect of nadroparine (Hommel et al. 1998). Further prospective outcome studies with LMWH failed to show any difference in functional outcome in the treated groups compared with placebo (Moonis and Fisher 2002). The TOAST trial randomized 1281 patients with acute stroke within 24 hours after onset of symptoms to receive either the low-molecular-weight heparinoid danaparoid or placebo (The Publications Committee for the TOAST Investigators 1998). Main outcome measure was a favorable outcome at 3 months or 7 days rated as the combination of a Glasgow Outcome Score of 1 or 2 and a modified Barthel Index of 12 or greater (on a scale of 0 to 20). Although there was a significant benefit for the active treatment group after seven days, this difference was not statistically significant after 3 months (which was the primary outcome time point of the study) with 75.2% of the danaparoid group and 73.7% of the placebo group having favorable outcomes ($p = 0.49$). There were significantly more symptomatic intracerebral hemorrhages in the active treatment arm (2.3% vs. 0.8%).

The TOPAS trial was a dose-finding study which compared 4 different doses of certoparin (3000 U anti-factor Xa once daily, 3000 U twice daily, 5000 U twice daily and 8000 U twice daily) given within 12 hours of stroke onset in a total of 404 patients (Diener et al. 2001). The trial included no placebo group. There was no correlation between the dose of certoparin and an improvement of neurological or functional outcome at 3 months. Severe bleeding tended to be more frequent in the highest dose group only. The TAIST study randomized 1486 patients with acute ischemic stroke to receive either high-dose tinzaparin (175 anti Xa IU/kg), low-dose tinzaparin (100 anti Xa IU/kg), or 300 mg aspirin within 48 hours

Table 1. Trials of LMWH in patients with acute ischemic stroke.

	FISS	FISS bis	TOAST	HAEST	TOPAS	TAIST
LMWH	nadroparine	nadroparine	danaparoid	dalteparin	certoparin	tinzaparin
Dose (U anti-Xa)	4100 once daily 4100 twice daily	85 U/kg once daily 85 U/kg twice daily	adjusted for anti-Xa level 0.6 to 0.8	100 U/kg twice daily	3000 once daily 3000 twice daily 5000 twice daily 8000 twice daily	100 U/kg once daily 175 U/kg once daily
Route of application	s.c.	s.c.	i.v.	s.c.	s.c.	s.c.
Control	placebo	placebo	placebo	ASS	-	ASS
Patients (n)	312	767	1281	450	800	1486
Inclusion interval (h)	48	24	24	30	12	48
Treatment period (d)	10	10	7	10	14	10
Follow up (months)	3	6	3	3	3	6
Primary endpoint	death or dependency	death or dependency	GCS and modified Barthel	Barthel Index, ischemic stroke	Barthel Index	modified Rankin Scale
Reference	Kay 1995	Hommel 1998	TOAST 1998	Berge 2000	Diener 2001	Bath 2001

after symptom onset (Bath et al. 2001). The primary outcome measure (assessed with the modified Rankin scale) was independence, disability or death at 6 months. The study found no difference in outcome between the three treatment groups. The HAEST trial was a randomized double-blind study which compared the efficacy of dalteparin (100 IU/kg subcutaneously twice daily) and aspirin (160 mg daily) in patients with acute ischemic stroke and atrial fibrillation (Berge et al. 2000). Treatment was started within 30 hours of stroke onset and continued for the first 14 days. At 3 months, there was no significant difference in outcome. The percentage of death or dependency was 66.1% in patients allocated to dalteparin and 64.8% in patients allocated to aspirin. Dalteparin was associated with a significantly higher frequency of extracerebral hemorrhages (5.8% vs. 1.8%).

Consistent with the results of these major trials of UFH and LMWH in acute ischemic stroke, a Cochrane systematic review based on twenty-one trials involving 23,427 patients (Gubitz et al. 2004), found no net short- or long-term beneficial effect on death or dependency associated with an immediate therapy with UFH, LMWH, heparinoids or oral anticoagulants in patients with acute ischemic stroke. Although a recent systematic review focusing on trials of LMWH in acute ischemic stroke observed a nonsignificant reduction in combined death and disability in patients treated with LMWH, this effect was again outweighed by increases in case fatality and symptomatic intracranial hemorrhage (Bath et al. 2000).

In conclusion, with the exception of one small study no controlled trial and no meta-analysis has yet demonstrated an improved outcome or a reduced mortality by UFH or LMWH therapy in patients with acute ischemic stroke. Currently, neither UFH nor LMWH can be recommended for the treatment of stroke-related morbidity.

Effect of Anticoagulation on Early Stroke Recurrence and in Different Stroke Subtypes

Although treatment with UFH or LMWH does not reduce stroke-related morbidity and mortality, anticoagulation may still be useful to prevent early stroke recurrence. In the IST study (International Stroke Trial Collaborative Group 1997), patients allocated to subcutaneous UFH had significantly fewer recurrent ischemic strokes within the first 14 days (2.9% vs. 3.8%) but this beneficial effect was offset by a similar-sized significant increase in hemorrhagic strokes (1.2% vs. 0.4%). In contrast, the significant decrease of recurrent stokes among aspirin-allocated patients (2.8% vs. 3.9%) was not offset by an increase of hemorrhagic strokes (0.8% vs. 0.9%). In the Cochrane systematic review of anticoagulants in patients with acute stroke (Gubitz et al. 2004), immediate anticoagulant therapy was associated with about 9 fewer recurrent ischemic strokes per 1000 patients treated. However, it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial hemorrhages.

Nevertheless, the increase in hemorrhagic strokes among heparin-allocated patients in IST should be viewed critically in regard to potential pitfalls of the trial. Computed tomography (CT) was not a requirement before study inclusion and more than 30% of all patients were randomized before a cerebral CT scan was obtained making it likely that patients with hemorrhagic strokes have been included. In addition, there was no systematic coagulation monitoring and several patients, particularly those receiving 12500 IU twice daily might have been outside the therapeutic range. A prospective study of patients with large cerebral embolic infarction receiving early anticoagulation with intravenous heparin showed that the risk of hemorrhagic worsening was significantly related to excessive prolongation of the activated partial thromboplastin time (aPPT). The authors recommended a rigorous coagulation monitoring to keep the aPTT at 1.5 to 2.0 times control values (Chamorro et al. 1995). While high-dose heparin was associated with a non-significant increase in early death or recurrent stroke and a definite excess of transfused or fatal extracranial bleeds in the IST study, low-dose heparin was associated with a significant decrease of early death or stroke (10.8% vs. 12.0%) without a significant excess of transfused or severe extracranial bleeds (International Stroke Trial Collaborative Group 1997).

Although the small overall reduction of recurrent ischemic stroke by heparin is offset by an equal-sized increase of symptomatic hemorrhage in general stroke populations, certain subtypes of stroke may carry a higher risk of recurrence and may benefit from early anticoagulant therapy. This has been suggested for patients with cardioembolic stroke and particularly for those with atrial fibrillation (AF).

Oral anticoagulant therapy is an established long-term prophylaxis of cerebral and systemic embolism in AF. Several primary prevention trials in patients with AF have shown that oral anticoagulants like warfarin and phenprocoumon reduce the risk of stroke by 60-70% (Atrial Fibrillation Investigators 1994). A prophylactic effect of equal magnitude was found for long-term oral anticoagulation after a stroke by a single secondary prevention trial (EAFT 1993), but the best time to start anticoagulant therapy could not be estimated as in most patients effective anticoagulation was obtained only weeks after their stroke. However, patients with acute stroke and AF have an increased risk of early recurrence which was estimated to be 10-20% within 14 days after stroke onset in observational studies (Cerebral Embolism Task Force 1989). In recent controlled stroke trials however, early stroke recurrence was substantially lower and reached 5-8% in patients treated with aspirin or placebo (Berge et al. 2000, Saxena et al. 2001, The Publications Committee for the TOAST Investigators 1998).

A first small randomized study that compared intravenous UFH with no antithrombotic treatment in 45 patients with cardioembolic stroke was terminated prematurely after two strokes and two hemorrhagic transformations had occurred in the control group (Cerebral Embolism Study Group 1983). Later studies, however, could not unequivocally demonstrate a benefit of early anticoagulation. In the International Stroke Trial, a total of 3169 patients with AF had been included and their outcome has been reported separately (Saxena et al. 2001). Although a clear and dose-dependent reduction in early recurrent ischemic stroke among patients treated with subcutaneous UFH was found, there was no net advantage to treatment with heparin as the frequency of hemorrhagic strokes was significantly increased and combined incidences of ischemic stroke and intracranial hemorrhage were about 5% in all treatment groups. In the HAEST study, which evaluated the efficacy of the LMWH dalteparin compared with aspirin in 449 patients with acute ischemic stroke and AF, rates of recurrent ischemic stroke (8.5% vs. 7.5%, $p = 0.73$) and frequencies of secondary brain hemorrhage (2.7% vs. 1.8%, $p = 0.54$) were each not different between treatment groups. Moreover, neither HAEST nor IST showed a benefit of anticoagulation on functional outcome or death in the subgroup of stroke patients with AF. In addition, none of the other trials of LMWH in acute stroke found a positive effect on these clinical endpoints in subgroups of patients with cardioembolic stroke (Berge et al. 2000, Hommel et al. 1998, Kay et al. 1995, The Publications Committee for the TOAST Investigators 1998). Thus, most authors come to the conclusion that heparin should not routinely be used for early anticoagulation in patients with AF and presumed cardioembolic stroke (Berge et al. 2000, Hart et al. 2002, Saxena et al. 2001).

Under pathophysiologic considerations, however, anticoagulation may be feasible for certain subgroups of stroke patients with presumed cardioembolism who are at particularly high risk for recurrence such as patients with mechanical heart valves or recent myocardial infarction with mural thrombi. Data regarding the relative risks and benefits of anticoagulants in these patients are lacking. Patients with dissection of the extracranial carotid or vertebral arteries may also benefit from early anticoagulation to prevent stroke recurrence due to artery-to-artery embolism arising from local thrombus formation at the site of dissection. Uncontrolled series showed a favorable outcome of patients who received early heparin treatment whereas those without suffered from severe stroke due to embolic middle cerebral artery occlusion (Sturzenegger 1995). The TOAST study did find a significant response to treatment with danaparoid at 7 days and 3 months among patients with stroke due to large-artery atherosclerosis which also suggests a possible benefit of anticoagulants in the prevention of artery-to-artery embolism. No benefit of danaparoid was observed among patients with stroke due to small-artery occlusion and unselected patients with presumed cardioembolic stroke (The Publications Committee for the TOAST Investigators 1998).

In conclusion, the routine use of UFH or LMWH to prevent early stroke recurrence cannot be recommended in patients with acute ischemic stroke. The reason for this negative recommendation is not only a general lack of proof of efficacy but also safety concerns about an unacceptable increase of severe bleeding complications, particularly cerebral hemorrhage. If early anticoagulation is initiated in a patient with a particular stroke subtype because of a pathophysiological rationale, the risk of bleeding complications must be minimized. This includes regular coagulation monitoring and the routine use of CT scans with strict exclusion of patients with hemorrhagic infarcts, large infarcts, and severe cerebral leukoaraiosis. Patients with systemic contraindications such as severe uncontrolled hypertension, uncorrected bleeding disorders or potential bleeding lesions should also been excluded from early anticoagulation.

Bridging Therapy from Acute to Long-term Anticoagulation

In clinical practice, it is a common proceeding to start heparin therapy in the first days after a TIA or a small cerebral infarct in patients with AF while overlapping oral anticoagulant therapy has not reached therapeutic INR levels. This proceeding has been described as "bridging therapy from acute to long-term anticoagulation" and a small study of 48 patients has compared the risk-benefit profiles of intravenous UFH and the LMWH enoxaparin in this setting (Kalafut et al. 2000). The authors found that fewer patients in the enoxaparin group experienced neurological worsening as compared with the UFH group (8% vs. 33%, $p < 0.05$) and that the rate of bleeding complications was lower. Moreover, the length of hospital stay and the total cost of care were reduced for enoxaparin treated patients. However, since all large prospective trials of UFH and LMWH in acute stroke and available meta-analyses have been negative and risk of early recurrence is lower than previously thought, the reasonability of a bridging therapy with any type of heparin must be questioned. Until recently, bridging with heparin was generally recommended because of the fear of creating a hypercoagulable state in patients with unrecognized protein C deficiency by starting oral anticoagulation alone. However, this fear has not been substantiated. Presently, to administer heparin before or at the same time as oral anticoagulants is only recommended in patients with a known protein C deficiency or other thrombophilic state (Ansell et al. 2001).

Prevention of Venous Thromboembolism after Ischemic Stroke

Venous thromboembolism (VTE) is a common complication and an important cause of death and

morbidity in acute ischemic stroke. Compared to other medical conditions, patients with stroke are at particularly high risk of VTE because of limb paralysis, prolonged immobility and increased prothrombotic activity. Deep vein thrombosis (DVT) was found in about 50% of stroke patients without prophylaxis in randomized trials using venography, ultrasonography or fibrinogen leg scanning (Geerts et al. 2001, Gubitz et al. 2004). Pulmonary embolism (PE), the most serious consequence of DVT, can result in significant morbidity and has been estimated to be responsible for approximately 5-13% of early deaths following stroke (Geerts et al. 2001, Mazzone et al. 2004).

Several trials have demonstrated that both UFH and LMWH are effective in reducing the risk of VTE in stroke patients. Aside from those trials which primarily studied outcome and stroke recurrence after ischemic stroke, numerous smaller studies specifically evaluated the efficacy of UFH and LMWH in the prophylaxis of DVT in patients with acute stroke. Pooled results of five trials of low-dose UFH demonstrated a 56% relative risk reduction in DVT relative to pooled control patients (Geerts et al. 2001). Similarly, results of three trials of LMWH showed a relative risk reduction in DVT of 58% for treated patients. In two trials directly comparing enoxaparin 40mg once daily to low-dose UFH, the LMWH enoxaparin provided greater protection from DVT without increasing risk of hemorrhage, with relative risk reductions favoring LMWH of 29% and 43%, respectively (Geerts et al. 2001, Harenberg et al. 1999, Hillbom et al. 1999). The low-molecular-weight heparinoid danaparoid was also effective in DVT prophylaxis compared to placebo and there was a relative risk reduction of 44% compared to low-dose UFH in 2 trials (Dumas et al. 1994, Geerts et al. 2001, Turpie et al. 1992).

All these studies on DVT prophylaxis after stroke focused on thrombi detected by sensitive diagnostic tests. However, most thrombi were asymptomatic or not clinically relevant and more major clinical endpoints like death, functional outcome, symptomatic PE and severe hemorrhage seem more appropriate for assessing the value of anticoagulant therapy in prevention of VTE in stroke patients (Geerts et al. 2001). Most of the already mentioned trials of heparin for the treatment of acute ischemic stroke evaluated frequency of VTE aside from major clinical endpoints. The largest trial so far, the International Stroke Trial, found a significant reduction in the frequency of fatal and symptomatic non-fatal PE, with an incidence of 0.8% in the non-treated group and 0.5% in patients treated with subcutaneous UF ($p=0.02$) (International Stroke Trial Collaborative Group 1997). In another large scale randomised trial which compared danaparoid with placebo, none of the treated patients experienced clinical significant VTE compared to an incidence of 0.4% in the placebo group (The Publications Committee for the TOAST Investigators 1998). However, in both trials heparin treatment did not improve the overall outcome of patients with acute ischemic stroke and at final follow up there was no difference in the proportion of patients dead or dependent as any reductions in recurrent ischemic stroke or PE were counterbalanced by similar-sized increases in intracranial and extracranial hemorrhages. Trials of LMWH produced similar results. In the only small trial that demonstrated a beneficial effect of the LMWH nadroparine on the clinical outcome of stroke patients at 6 months (FISS), frequencies of VTE were to low to detect any relevant difference between treatment groups (Kay et al. 1995) and the overall positive effect of nadroparine was not confirmed in the later FISS bis trial (Hommel et al. 1998). In two recent outcome trials of LMWH in acute stroke, there was no overall benefit on the primary clinical endpoints (Bath et al. 2001, Berge et al. 2000). Although no DVT occurred in patients treated with high-dose tinzaparin in the TAIST trial (Bath et al. 2001), this benefit was again offset by an increased rate of intracerebral hemorrhage and overall there was no difference in PE, stroke recurrence, death and functional dependency between patients treated with aspirin, high-dose and low-dose tinzaparin. In the HAEST study on dalteparin in patients with acute stroke and AF (Berge et al. 2000), the frequency of VTE was non-significantly lower in the group of patients treated with dalteparin (0.4% compared to 2.2% in patients treated with aspirin, $p=0.22$), but more severe hemorrhages occurred in the dalteparin group and no effect on stroke recurrence and outcome was found.

In the Cochrane systematic review of anticoagulants in patients with acute stroke (Gubitz et al. 2004), treatment with UFH, LMWH, heparinoids or oral anticoagulants was associated with a significant reduction in DVT from 44% in controls to 15% in treated patients. The absolute reduction on DVT with anticoagulation was substantial with 281 DVTs prevented per 1000 patients treated. However, only 916 patients from 10 trials (3.9% of all patients included) were systematically studied to determine the effect of anticoagulants on the occurrence of symptomatic or asymptomatic DVT. Moreover, anticoagulant therapy was also associated with a 9 per 1000 increase in symptomatic intracranial hemorrhages. Similarly, anticoagulants avoided about 4 pulmonary emboli per 1000, but this benefit was offset by an extra 9 major extracranial hemorrhages per 1000 treated patients.

Similar to the results of the Cochrane meta-analysis, the recent systematic review focusing on trials of LMWH in acute ischemic stroke by Bath et al. found that LMWH therapy lowered the frequency of DVT and symptomatic PE but increased the risk of major extracranial bleeding (Bath et al. 2000). In another Cochrane systematic review of five small trials directly comparing LMWH with UFH in patients with acute ischemic stroke LMWH treatment decreased the occurrence of DVT from 22% to 13% but too few data were available to provide a reliable estimate of

more important clinical outcomes. However, the existing data on LWMH in acute stroke are consistent with results of studies in the prevention of perioperative thrombosis and in the treatment of DVT which also found LMWH to be superior to UFH in terms of efficacy and safety (Geerts et al. 2001, Leizorovicz et al. 1992, Lensing et al. 1995).

On the grounds of trial results, treatment guidelines and consensus statements recommend both low-dose UFH and LMWH for DVT prophylaxis only for those patients with acute ischemic stroke with impaired mobility or other factors determining a particular high risk of VTE (Adams et al. 2003, Geerts et al. 2001, The European Stroke Initiative 2003). However, unlike the missing benefit of both LMWH and UFH on overall clinical outcome, data from several individual trials and meta-analyses suggest a superiority of LMWH over UFH with respect to DVT prophylaxis which is reflected in the current clinical praxis on German stroke units. In a recent published survey on coagulation therapy in acute stroke patients from all major stroke units in Germany, the majority of participants reported to use LMWH for prophylaxis of venous thromboembolism (Daffertshofer et al. 2003).

Anticoagulation in Patients with Cerebral Venous and Sinus Thrombosis

Anticoagulation has shown to be effective in the treatment of patients with extracerebral venous thrombosis and its use has also been advocated in patients with cerebral venous thrombosis after the first report of successful heparin therapy by Stansfield in 1942. However, since intracranial hemorrhage occurs in 30-50% of patients with cerebral venous and sinus thrombosis (CVST), many neurologists hesitated to use heparin because they feared that anticoagulation may either promote intracranial hemorrhage or cause clinical deterioration if intracranial hemorrhage is already present. Since Stansfield`s initial publication, there have been numerous reports of dramatic improvement in patients receiving anticoagulants (for review see Einhäupl and Masuhr 1994) and today there are data available from two controlled trials which favor the use of anticoagulants in patients with CVST because it may reduce the risk of a fatal outcome and severe disability and does not promote intracranial hemorrhage (Einhäupl et al. 1991, de Bruijn et al. 1999).

In the prospective study of Einhäupl and coworkers which compared dose-adjusted intravenous heparin with placebo in 20 patients, 8 patients in the heparin group recovered completely and none died whereas only one patient in the placebo group recovered fully and 3 patients died. Three patients with previous intracranial hemorrhage recovered completely and no new hemorrhages occurred in the heparin group whereas in the placebo group 2 patients with pre-treatment hemorrhage died and 2 new intracranial hemorrhages were observed.

The safety and good responsiveness of patients with CVST to anticoagulant therapy even in the presence of intracranial hemorrhage may be explained by the underlying pathophysiolgy (Villringer et al. 1994). Venous thrombotic occlusion causes an increase of venous and capillary pressure which promotes the diapedesis of erythrocytes into the brain parenchyma. Therefore, persistence of thrombosis is the key mechanism of CVST-related hemorrhage. Heparin therapy prevents further propagation of thrombosis and reocclusion of recanalized (due to endogenous lysis) venous vessels. Capillary pressure decreases after recanalization which prevents further diapedesis of erythrocytes. This may explain the reduction of intracranial hemorrhage in patients with CVST during heparin treatment (see Fig. 1).

The effectiveness of body weight adjusted low-molecular-weight heparin has been studied in a second randomized treatment trial (de Bruijn et al. 1999). The authors compared nadroparine (180 anti Xa U/kg per 24 hours administered by 2 daily subcutaneous injections) with placebo in 60 patients with CVST. A poor outcome - defined as death or Barthel index <15 - was observed after 3 weeks in 6 of the 30 patients treated with LMWH (20%) compared to 7 of the 29 controls (24%). After 12 weeks, 3 patients (10%) in the LMWH group and 6 patients (21%) in the placebo group had a poor outcome which corresponded to a non-significant absolute risk reduction of 11% in favor of the active treatment. No new intracranial hemorrhages or secondary worsening of the 15 patients with pre-treatment hemorrhage were observed in the LMWH group. A meta-analysis of the two therapy trials (de Bruijn et al. 1999) showed that the use of anticoagulants led to an absolute risk reduction in mortality of 14% and in death or dependency of 15% with relative risk reductions of 70% and 56%, respectively. Although this difference was not statistically significant (presumably due to the small sample size with a total of 79 patients) both trials showed a consistent and clinically meaningful trend in favor of anticoagulation and demonstrated the safety of anticoagulant therapy.

In conclusion, the available data reinforce the use of heparin as first-line treatment of CVST. However, it is unclear, whether treatment with full-dose intravenous heparin or subcutaneously applied LMWH is equally effective since there is no study which has compared these two treatment regimes. We recommend the use of intravenous heparin in critical ill patients because the aPTT may normalize within 1 h after discontinuation of the infusion if complications occur or surgical intervention is necessary. However, in less severe cases (e.g. ambulatory patients) treatment with subcutaneously applied LMWH may be feasible.

Conclusion

Currently, all patients with acute ischemic stroke should receive aspirin to reduce stroke-related

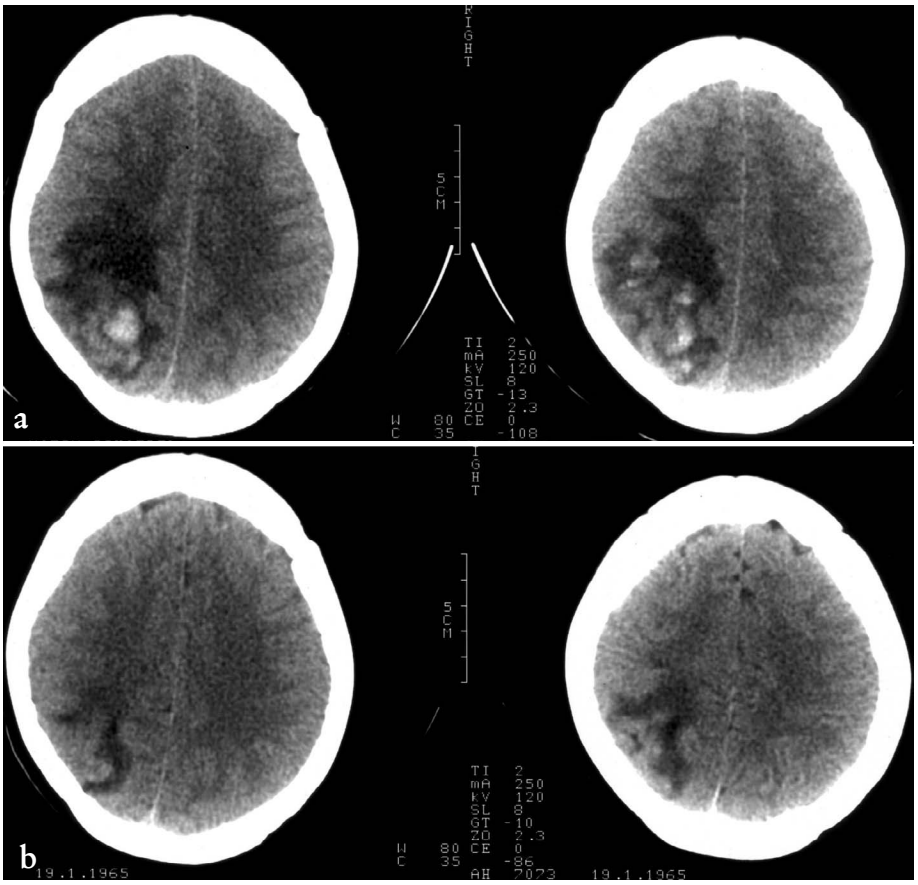

Fig. 1. Unenhanced cerebral computed tomography showing right-sided multiple small hemorrhages within a large hypodensity. Typical aspect of a hemorrhagic infarct with associated edema in a patient with extended thrombosis of the superior sagittal sinus (a). Reduction of the previous small hemorrhages and the associated edema after 14 days of intravenous full-dose anticoagulation (b).

morbidity and mortality unless there are contraindications such as allergy and gastrointestinal bleeding. The use of UFH or LMWH cannot be recommended except for the prevention of deep vein thrombosis in patients with impaired mobility or other factors determining a high risk for venous thromboembolism if risk of bleeding is minimized. In such patients, the concurrent use of low-dose LMWH and aspirin may be a feasible option and is already the preferred therapeutic concept on most German stroke units (Daffertshofer et al. 2003). Further clinical research should aim at the identification of stroke subgroups who carry a particular high-risk for stroke recurrence and may benefit from early anticoagulation with UFH or LMWH.

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Address for correspondence:
Dr. med. Florian Masuhr
Department of Neurology
Charité Medical School
Humboldt-University
Schumannstrasse 20/21
D-10117 Berlin, Germany
Phone: +49-30-450 560074
Fax: +49-30-450 560932
E-mail: Florian.Masuhr@charite.de