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Abstract

Anticoagulant therapy has been anticipated to increase risk of cerebrovascular complications (CVC) in native valve endocarditis (NVE). This study investigates the relationship between ongoing oral anticoagulant therapy and incidence of symptomatic CVC in left-sided NVE. In a prospective cohort study CVC incidence was compared between NVE patients with and without ongoing warfarin. Among 587 NVE episodes, 48 (8%) occurred in patients on warfarin. A symptomatic CVC was seen in 144 (25%) patients with only 3 on warfarin. CVC were significantly less frequent in patients on warfarin (6% vs. 26 %, OR 0.20, 95% CI 0.06-0.6, p=0.006). No increase in haemorrhagic lesions was detected in patients on warfarin. *Staphylococcus aureus* aetiology (adjusted OR 6.3, 95% CI 3.8-10.4), and vegetation length (adjusted OR 1.04, 96% CI 1.01-1.07) were risk factors for CVC while warfarin on admission (adjusted OR 0.26, CI 95% 0.07-0.94), history of congestive heart failure (adjusted OR 0.22, 95% CI 0.1-0.52) and previous endocarditis (aOR 0.1, 95% CI 0.01-0.79) correlated with lower CVC frequency.

Introduction

Anticoagulant therapy in infective endocarditis (IE) has been controversial since the early experiences of combination therapy with antibiotics and heparin in the 1940s. A high risk of cerebral haemorrhage was seen in most studies [1, 2] and the addition of anticoagulant therapy was shown unnecessary when adequate penicillin doses were administered [3]. Anticoagulants as a part of IE therapy was discouraged [4, 5] but later the recommendations to some extent was modified in patients with other indications for anticoagulant therapy [6]. Modern guidelines agree that IE *per se* is not an indication for anticoagulant therapy, but varying recommendations are given concerning ongoing anticoagulant therapy at the time of IE diagnosis [7-9]. Current guidelines are based on experiences from the early years of IE treatment, retrospective studies mainly involving patients with prosthetic valve endocarditis (PVE) [10-12], and the opinions of authorities in the field [5, 6]. Recommendations concerning native valve endocarditis (NVE) are few [7]. More recent studies addressing cerebral events in IE show that hemorrhagic complications are relatively rare in both NVE and PVE [13-15] but carry a risk of excess mortality.

In our clinical experience, the risk of haemorrhagic cerebral complications in patients already on anticoagulants when IE is diagnosed is not as high as earlier described [6, 10] and different mechanisms for embolism in native and prosthetic valve endocarditis are possible. Based on these considerations, the aim of this study was to investigate the relationship between ongoing oral anticoagulant therapy with vitamin K antagonists and the incidence of symptomatic cerebrovascular complications (CVC) in patients with left-sided NVE. A secondary aim was to evaluate clinical variables associated with CVC in NVE.

Methods

Study population

Data were obtained from 866 consecutive episodes of IE treated at one university hospital in Gothenburg (Sweden) from January 1996 to January 2008 and at two university hospitals in Copenhagen (Denmark) from October 2002 to January 2008. Left-sided NVE was seen in 587 IE episodes in 570 patients, and these episodes formed the study group. IE was classified as definite in 510 (87%) of the episodes according to the revised Duke criteria.

Patients were included prospectively in the study and demographic, microbiological, echocardiographic, radiological and clinical features were registered in a database. Patients were treated at the Cardiology Department (Denmark) or the Infectious Diseases Department (Sweden), and consultations with other specialists including thoracic surgeons, were performed regularly and, when needed, on an emergency basis. Transoesophageal echocardiography was performed in 98% of the episodes; in the remaining episodes only transthoracic examination was possible due to early in hospital death. Presence of vegetation, maximum vegetation length and localization were registered, as well as signs of paravalvular involvement. Antibiotic and surgical therapy was given according to guidelines. Individual decisions regarding anticoagulant therapy were made by the treating physician.

Cerebrovascular complications

Patients with neurological symptoms on admission or during treatment for NVE were examined using cerebral computed tomography (CT) or magnetic resonance imaging (MRI) and lumbar puncture if indicated. Symptomatic CVC were classified as ischemic and hemorrhagic strokes, subarachnoid and intracerebral haemorrhage, transient ischemic attacks (TIA), and cerebral infections (meningitis and cerebral abscesses). . Subclinical cerebral embolism was not investigated for.

Anticoagulant therapy

Ongoing oral anticoagulant therapy was defined as prescribed, and reported continuous use of an oral anticoagulant prior to admission for IE. The only oral anticoagulant agent used among study patients was warfarin, a widely used vitamin K antagonist. To assess intensity of anticoagulation International Normalized Ratio (INR) was measured during the first day of admission in patients with ongoing warfarin therapy, but INR was not regularly measured in patients without such therapy. Discontinuation of warfarin was registered, as was

replacement therapy with low molecular weight heparin.

Statistical analyses

The primary outcome variable was CVC established at admission or occurring during antibiotic treatment in patients with left-sided NVE. The patients were divided into two groups based on whether or not they were receiving warfarin at the time of admission. Between-group comparisons of categorical variables were performed using a Chi-square test or Fischer's exact test when appropriate. Continuous variables were compared using Mann-Whitney U test, and were expressed as median and interquartile (IQR) range. A multivariate logistic regression model was used to assess the independent relationship between baseline variables and CVC incidence. Baseline variables included in the analyses were age, sex, history of diabetes mellitus, haemodialysis, congestive heart failure, previous IE or intravenous drug abuse, malignancy, immunosuppression, atrial fibrillation on admission, presence and maximum length of vegetation, affected valve (mitral versus aortic), maximum C-reactive protein (CRP) level, ongoing medication with warfarin or acetylsalicylic acid (ASA) and microbiological aetiology. Variables with a univariate p-value of ≤ 0.05 were included in the multivariate analysis. Statistical analyses were performed using SPSS version 16.0.

Results

Patient characteristics

Among the 587 NVE episodes studied, 48 (8 %) occurred in patients who were receiving warfarin at the time of admission (table I). Atrial fibrillation on admission was documented in 83 out of 587 episodes of NVE (14%). Eighteen of the 83 patients (22%) with documented atrial fibrillation on admission for NVE were on warfarin. Warfarin use was significantly more common in episodes with atrial fibrillation at the time of NVE diagnosis than in episodes without atrial fibrillation (18/48, 38% vs. (65/539, 12%, $p<0.001$). Patients on warfarin had a higher prevalence of congestive heart failure prior to NVE diagnosis and tended to be older (median age 69 years vs. 64 years, $p=0.058$)

The prevalence of diabetes mellitus, haemodialysis and immunosuppression did not differ significantly between the groups nor did the presence or valvular localization of vegetations detected by echocardiography. Vegetations tended to be smaller among patients on warfarin (8 vs. 10 mm, $p=0.05$). Frequency of cardiac surgery during antibiotic treatment did not differ significantly between the groups (46% vs. 44%) nor did in-hospital mortality (10% vs. 12%). There was a male predominance in the cohort (68% men) but the proportions of men and women receiving warfarin did not differ significantly. Enterococcal NVE was significantly more frequent in the warfarin treated group (23% vs. 12%, $p=0.03$), but other microbiological aetiology did not differ significantly (table II).

Cerebrovascular complications

A symptomatic CVC was seen in 144 (25%) of the 587 NVE episodes, and neurological symptoms were present on admission in 74% (107/144) of these. Ischemic infarction was seen in 96 episodes (67%) and cerebral infection, mainly meningitis, in 38 episodes (26%) with CVC. Cerebral haemorrhage occurred in 14 (10%) of the episodes with a CVC, including haemorrhagic infarction in six and ruptured mycotic aneurysms in two episodes (table III). More than one type of cerebral lesion was documented in 26 out of 144 patients with CVC (18%).

Oral anticoagulants and cerebrovascular complications

CVC was seen significantly less frequently in patients on warfarin than in patients without this treatment, 6% (3/48) vs. 26% (141/539), unadjusted odds ratio (OR) 0.2, 95% CI 0.06-0.6, $p=0.006$ (figure 1). The pattern with lower incidence of CVC among NVE patients on warfarin was seen for all microbiological aetiologies, but the difference was significant only for *Staphylococcus aureus* NVE. Of the patients with ongoing warfarin treatment

suffering a symptomatic CVC, the microbiological aetiology was *Staphylococcus aureus* in two cases and group B streptococci in one case. Among the 48 warfarin treated patients all three CVC were already established on admission for NVE and no new CVC occurred after the start of antibiotics. Among the 539 patients not on warfarin on admission for NVE, a CVC (first time or recurrent) occurred during antibiotic treatment in 37 patients (7 %). The majority of the CVC developing after adequate antibiotic therapy was initiated were ischemic infarctions found in 29 patients, while cerebral infections were found in three patients and TIA or cerebral haemorrhage in two patients respectively.

The frequency of haemorrhagic complications among patients with and without warfarin on admission for NVE was 2 % in both groups (1/48 and 13/539, respectively). Warfarin was discontinued within the first days of IE treatment in 19 (40 %) of the episodes and replaced by low molecular weight heparin in 7 of these. One of three patients on warfarin with a CVC displayed a hemorrhagic infarction, and warfarin was discontinued on the first day of admission. Warfarin was continued in the other two patients with CVC, who were diagnosed with an ischemic lesion in one case and a brain abscess in the other. All three patients survived in-hospital treatment. Median INR on admission was 2.0 (IQR 1.5-2.4) in the 48 patients on warfarin. INR was also registered in 80 patients not on current warfarin therapy and median INR was 1.2 (IQR 1.1-1.4) in that group.

Risk factor analysis for cerebrovascular complications

In the logistic regression analyses (table IV) ongoing warfarin therapy on admission for NVE was independently associated with a lower frequency of CVC, adjusted odds ratio (aOR) 0.26, CI 95% 0.07-0.94, p=0.04. *Staphylococcus aureus* aetiology was a risk factor for CVC with an aOR of 6.3 (95% CI 3.8-10.4, p<0.001). History of congestive heart failure was associated with fewer CVC (aOR 0.22 95% CI 0.1-0.53, p=0.001) as was a history of a previous IE (aOR 0.1, 95% CI 0.01-0.79, p=0.03). Longer vegetations detected by echocardiography correlated to a higher CVC frequency (aOR 1.04, 1.01-1.07, p=0.005) No statistical significant difference was found between maximum length of vegetation in episodes with CVC established on admission as compared with episodes with CVC occurring during antibiotic therapy (data not shown).

Discussion

Cerebrovascular events in IE are common and associated with unfavourable prognosis. Several reports on haemorrhagic side effects of anticoagulant therapy in IE patients suffering cerebral complications have been published [5, 6, 10, 16]. Experimental studies on anticoagulant effects in IE pathogenesis are few [17, 18] and empirical data do not support the initiation of anticoagulant therapy once IE is diagnosed. The difficult issue is dealing with ongoing anticoagulation therapy at the time of diagnosis of IE. Recommendations concerning this are based on low level evidence in guidelines dealing with the management of IE [7, 9] Therefore, clinicians have little information available to inform a decision regarding continuation of anticoagulation in this situation. However, the number of individuals on anticoagulant therapy is rising [19]. The present study addresses the relationship between ongoing oral anticoagulant therapy during development of NVE and the incidence of CVC in a large prospective cohort. This design was intended to eliminate confounding from inherent differences in CVC rate between NVE and PVE. Since IE is a relatively rare disease a randomized trial to evaluate this question is not possible. The majority of cerebral complications have already occurred when IE is diagnosed (74% in the present series) and the intention was not to evaluate the effect of initiation of warfarin therapy after NVE diagnosis, which would be better addressed in a randomized trial.

After multivariate modelling a lower risk of CVC prevailed in patients with ongoing warfarin treatment on admission for NVE (aOR 0.26, 95% CI 0.07-0.94, p=0.04) compared to patients not on warfarin. The difference was seen among non-hemorrhagic intracerebral events, while hemorrhagic events were uncommon in both groups. A lower rate of CVC in anticoagulated patients with NVE contradicts the results in a previous retrospective study separately addressing the issue of cerebrovascular accidents in NVE patients on anticoagulant therapy [6]. In that study cerebral bleeding was seen in 5% of the NVE patients and infarctions in 7%, which is a relatively low number of ischemic events compared to other series. A decreasing risk of intracranial haemorrhage over time in PVE patients on anticoagulant therapy has been found [20], contrary to the increasing frequency of anticoagulant associated intracerebral haemorrhage reported during the 1990s in patients with anticoagulant therapy for any indication [21].

The frequency of cerebral haemorrhage was low among our patients, which is in accordance with recent IE studies [15, 22]. The high proportion of anticoagulant associated cerebral haemorrhages found by Tornos et al. [10] in *Staphylococcus aureus* PVE was not reproduced in this study of NVE. The median INR the first day of admission was 2.0 so almost half of the values were lower than the therapeutic range (2.0-3.0). This might have contributed to some degree to the low frequency of cerebral hemorrhagic complications seen among our patients

on anticoagulant therapy.

After admission for IE, warfarin was continued in 60% of the patients, discontinued in 40%, and replaced with low molecular weight heparin in one third of these. Irrespective of what decision was taken regarding the warfarin treatment no CVC was seen in the warfarin group after the initiation of antibiotic treatment. Among patients not on warfarin, the CVC frequency after initiation of antibiotic treatment was 7%. The low frequency of cerebral emboli after initiation of antibiotics is well known [23] and emphasizes that early diagnosis of IE is of major importance to reduce the number of cerebral complications.

The definition of CVC used in this study was based on the assumption that both infectious and non-infectious cerebral complications in IE have a common pathogenetic pathway through septic embolism from vegetations. Ischemic stroke with focal neurological symptoms is the most frequently reported cerebral complication in IE but also well-documented are more complex syndromes with varying combinations of focal neurological signs, meningism and encephalopathy in the same patient as well as silent cerebral embolism [5, 14, 24, 25]. Autopsy data have indicated that embolic meningoencephalitis is the fundamental neuropathological change in IE [26] and a continuum between vascular and infectious cerebral complications in endocarditis has been suggested [27, 28]

Staphylococcus aureus aetiology was a major risk factor for CVC in our study as has been shown previously [22]. Vegetation length was associated with a higher frequency of cerebral complications, but since most CVC were established before the first echocardiographic examination was performed, the implications of this finding to reduce the number of CVC in IE patients are limited. However, vegetation length can also be used as a prognostic marker in IE and has in other studies been correlated to an increased frequency of embolic events during antibiotic treatment [29]. Median vegetation length in patients on warfarin was 8 mm as compared with 10 mm in patients not using warfarin ($p=0.05$). Warfarin induced lower levels of vitamin K dependent coagulation factors might impact on the formation and dynamics of vegetations and give a protective effect on CVC risk through this mechanism. Lower rates of embolism has also been observed in PVE patients [30], where most patients are on warfarin at the time of IE. Additional beneficial influence of warfarin treatment on cerebral embolic risk can be hypothesized, e.g. through separate fibrin interactions [17]. Another indirect effect of warfarin treatment is regular INR follow-up, which might shorten the duration of symptoms before admission for NVE. A history of congestive heart failure and previous IE episode was associated with a lower risk of CVC in the study cohort. Possible explanations for this could be better access to health care facilities and higher diagnostic awareness of concomitant cardiac conditions in this type of patients. However, the observed relation

between history of congestive heart failure and lower CVC incidence among NVE patients is of unknown significance and could represent confounding due to variables not registered (i.e. use of other cardiac medication such as statins or angiotensin-converting enzyme inhibitors) or a chance finding. Regarding individuals who have experienced a previous IE shorter diagnostic delay is possible.

Patients on warfarin tended to be older and had a higher frequency of enterococcal NVE as compared with patients not on warfarin. Fewer CVC among warfarin treated patients was seen for all microbiological aetiologies, but the difference was significant for episodes caused by *Staphylococcus aureus* only, as separately described [31]. This uniform pattern irrespective of NVE causative organism supports the results of the multivariate analysis with an independent association between warfarin use and lower CVC incidence. Warfarin treated patients had also a higher frequency of atrial fibrillation on admission. This was expected since atrial fibrillation is an important indication for anticoagulation. Among patients with atrial fibrillation, only one fifth were on warfarin on admission for IE. This figure might reflect a high proportion of new atrial fibrillation induced by fever or heart failure associated with the current NVE episode or patient characteristics not elucidated in the study. Atrial fibrillation was not significantly associated with cerebral emboli among our patients, but the power of the present study was insufficient to evaluate differences in an expected excess embolic frequency of 5-10% per year.

Several limitations of our study must be acknowledged. First, this is a non-randomized observational study and despite prospective enrolment unmeasured variables may bias our results. Second, since the number of patients on warfarin treatment is relatively low and the number of events in this group is only three, misclassification or other bias might influence the results of the analyses. Therefore, our findings must be considered preliminary and revaluated in other studies. Third, individual indications for warfarin was not registered in the study protocol and during the 12-year study period the use of anticoagulation in patients with NVE may have changed. Fourth, the generalisability to other NVE populations must be questioned, since warfarin treatment and follow-up as well as IE treatment and prognosis is influenced by multiple factors, such as health care accessibility, age structure and health status of the population at risk, microbiological resistance patterns and proportion of surgically treated patients. Previous studies have shown relatively low IE related in-hospital mortality rates in Scandinavian populations [32] as compared with mortality in other regions of the world [33]. Influence of referral bias also limits the comparability of results in different studies.

In conclusion, there was no increased risk of haemorrhagic complications in patients with NVE continued on warfarin in this study population. This finding needs to be confirmed by other investigators before more specific

recommendations can be made but suggests that clinicians may cautiously continue ongoing anticoagulation in patients with NVE with or without CVC other than haemorrhagic brain lesions. The reduced risk of ischemic cerebral complications with ongoing anticoagulation in patients with left-sided NVE also needs to be confirmed by other investigators.

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34. **Table I.** Clinical characteristics among patients with native valve endocarditis. Groups divided by use of warfarin on admission.

Variable	Not using warfarin N=539 (%)	Using warfarin N=48 (%)	P
Female sex	175 (32)	15 (31)	> .30
Definite infectious endocarditis	469 (87)	41 (85)	> .30
Age (median) years (IQR)	64 (50-75)	69 (59-77)	0.058
Diabetes mellitus	66 (12)	7 (15)	> .30
Haemodialysis	23 (4)	2 (4)	> .30
History of congestive heart failure	77 (14)	15 (31)	0.002
Previous infective endocarditis	29 (5)	4 (8)	> .30
Atrial fibrillation on admission	65 (12)	18 (38)	<.001
History of malignancy	42 (8)	2 (4)	> .30
Immunosuppression	56 (10)	8 (17)	0.18
Intravenous drug use	23 (4)	1 (2)	> .30
Mitral valve involvement	289 (54)	27 (57)	> .30
Aortic valve involvement	297 (55)	26 (54)	> .30
Vegetation detected by echocardiography	409 (79)	37 (78)	> .30
(N=562)			
Length of vegetation (median) mm (IQR)	10 (5-14)	8 (4-11)	0.05
CRP maximum level (median) mg/L (IQR)	118 (68-206)	119 (60-180)	> .30
Receiving acetylsalicylic acid	122 (23)	7 (15)	0.20
Surgery	238 (44)	22 (46)	> .30
Mortality	68 (12)	5 (10)	> .30

CRP: C-reactive protein, IQR: interquartile range

Table II. Microbiological aetiology in 587 left-sided native valve endocarditis episodes in patients with or without warfarin on admission.

Variable	Not using warfarin N=539 (%)	Using warfarin N=48 (%)	P
Staphylococcus aureus	132 (24)	10 (21)	> .30
Viridans group streptococci	183 (34)	17 (35)	> .30
Enterococci	65 (12)	11 (23)	0.03
Other streptococci	39 (7)	3 (6)	> .30
Coagulase-negative staphylococci	32 (6)	2 (4)	> .30
Blood culture negative	57 (11)	4 (8)	> .30
Miscellaneous	31 (6)	1 (2)	0.28

Table III. Types of cerebral lesions in 144 native valve endocarditis episodes with cerebrovascular complications.

Variable	Number of episodes with CVC N=144 (%)	Proportion of all NVE episodes (N=587) %
CVC established on admission	107 (74%)	18%
Ischemic infarction	96[1] (67%)	16%
Cerebral infection	38 [1] (26%)	6%
Haemorrhagic lesion	14 [1] (10%)	2%
Transient ischemic attack	20 (14%)	3%
Mycotic aneurysm	2 (1%)	0.3%
More than one type of cerebral lesion	26 (18%)	4%

CVC: cerebrovascular complication, NVE: native valve endocarditis, [1] one patient with ongoing warfarin use

Table IV. Variables associated with cerebrovascular complications in 587 episodes of native valve endocarditis. Univariate and multivariate risk factor analysis

OR: odds ratio, CI: confidence interval, NVE: native valve endocarditis, IE: infective endocarditis, CRP: C-reactive protein

Variable	**Univariate logistic regression**		**Multivariate logistic regression**	
	OR (95 % CI)	**P**	**Adjusted OR (95 % CI)**	**P**
Staphylococcus aureus	5.8 (3.8 – 8.8)	<0.001	6.3 (3.8 – 10.4)	<0.001
Receiving warfarin at NVE diagnosis	0.2 (0.06 – 0.6)	0.006	0.26 (0.07 – 0.94)	0.04
History of congestive heart failure	0.3 (0.14– 0.59)	0.001	0.22 (0.1 – 0.52)	0.001
Previous IE episode	0.1 (0.01 – 0.66)	0.018	0.1 (0.01 – 0.79)	0.03
Vegetation detected by echocardiography	2.5 (1.5 – 4.4)	0.001	-	-
Length of vegetation (median)	1.05 (1.03 – 1.08)	<0.001	1.04 (1.01 -1.07)	0.005
CRP maximum level (median)	1.004 (1.00 –1.006)	<0.001	1.0 (0.99 – 1.01)	0.20
Female sex	1.3 (0.9-1.9)	0.19	0.9 (0.54 – 1.4)	>0.30
Age	0.99 (0.98-1.01)	>0.30	0.99 (0.98-1.01)	>0.30

Figure I. Frequency of cerebrovascular complications in 587 left-sided native valve endocarditis episodes in patients with or without warfarin.