Infective Endocarditis Due to *Staphylococcus aureus*

Deleterious Effect of Anticoagulant Therapy

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**Background:** The use of anticoagulant therapy in patients with infective endocarditis (IE) is a controversial issue.

**Objective:** To study the impact of anticoagulant therapy on the clinical outcome, mortality, and cause of death in a series of patients with native and prosthetic left-sided *Staphylococcus aureus* IE.

**Methods:** This report is based on all consecutive cases of IE diagnosed at our hospital between 1975 to 1997. Clinical data, including the use of anticoagulant therapy at the time of diagnosis, were prospectively obtained, and antibiotic treatment and surgical indications were uniform throughout the study period. Computed tomographic scans of all clinical records were reviewed.

**Results:** Of 637 consecutive patients with IE, 56 had left-sided *S aureus* IE affecting native valves in 35 patients and prosthetic valves in 21 patients. Of the patients with prosthetic valve IE, 19 (90%) were taking oral anticoagulant therapy at the time of diagnosis while no patient with native valve IE was receiving such treatment. There were no differences between native valve IE and prosthetic valve IE in age, sex, embolic episodes, and number of central nervous system complications. Mortality was higher in prosthetic valve IE than in native valve IE (71% vs 37%; *P* = .02). No patient with native valve IE died due to central nervous system complications, while 73% (11 of 15 patients) with prosthetic valve IE died due to central nervous system complications. The difference in the distribution of the type of death (stroke vs other) was significant (*P* < .007).

**Conclusions:** Our results suggest that in left-sided *S aureus* IE anticoagulant therapy is closely associated with death due to neurologic damage. According to our data, as soon as the clinical diagnosis of *S aureus* IE is indicated the use of anticoagulant therapy should be immediately stopped until the septic phase of the disease is overcome.

**Arch Intern Med.** 1999;159:473-475

NEUROLOGIC complications are a major determinant of a poor clinical outcome in infective endocarditis (IE). Among IE caused by the most frequent microorganisms, IE caused by *Staphylococcus aureus* affecting left-sided valves carries the worst prognosis and has a high prevalence of embolic episodes and neurologic involvement. It is also well known that prosthetic valve IE has a poorer prognosis than native valve IE. A previous study from our group on prosthetic valve IE showed that patients with infection due to *S aureus* died more often from neurologic complications than other patients with prosthetic valve IE due to other microorganisms.

The present study reviews a 22-year experience with left-sided IE caused by *S aureus* on native valves and valvular prostheses, with special emphasis on the outcome, the central nervous system complications, and the impact of anticoagulant therapy on mortality during the acute phase of the infection.

**RESULTS**

A total of 637 consecutive patients were diagnosed as having IE at our hospital between 1975 to 1997. Of those, 436 patients (68%) had left-sided IE and 201 (32%) had right-sided IE (intravenous drug users). Left-sided IE occurred in native valves in 314 patients (49%) and in prosthetic valves in 122 patients (19%) and was caused by *S aureus* in 56 patients (13%).

The study population included 56 patients with left-sided IE due to *S aureus*. There were 34 male and 22 female patients with ages ranging from 14 to 79 years, with a mean ± SD age of 52 ± 18 years. Thirty-five patients had native
PATIENTS AND METHODS

This report is based on all consecutive patients diagnosed at our hospital as having IE between 1975 and 1997. The identification of cases of IE was based on those patients whose conditions were diagnosed in the departments of cardiology or internal medicine as well as those diagnosed at necropsy before a clinical diagnosis was made. The diagnosis of IE was made according to clinical and echocardiographic data; all records have been reviewed and the new criteria proposed by Durack et al11 have been retrospectively applied. All patients included in the present analysis fulfilled the criteria of definite IE. Identification and antibiotic susceptibility test for S aureus were performed using standard methods. Clinical data were prospectively obtained and patients were uniformly treated according to antibiotic protocols.

Throughout the study period, surgery was recommended and performed if feasible in all patients with IE of prosthetic valves due to S aureus; in patients with IE of native valves due to S aureus, surgery was also promptly indicated if the sepsis was not quickly controlled and in cases of severe valvular destruction leading to heart failure or recurrent embolism.

The following data were listed: age, sex, predisposing heart disease, use of oral anticoagulant therapy on admission, presence and type of embolic events, type of neurologic complication, surgical treatment during the active phase of the infection, and outcome. Computed tomographic (CT) scans in all records were also reviewed and central nervous system complications were classified on the basis of clinical findings and/or CT scans into 4 types: cerebral hemorrhage, ischemic stroke, unruptured mycotic aneurysms, or central nervous system infection, including meningitis and intracranial abscesses.

Categorical variables were analyzed by univariate analysis with the χ² test, and continuous variables were analyzed with the Mann-Whitney U test. All tests were 2-tailed, and a P value of .05 was considered significant. All statistical analysis were performed using statistical software (SPSS; SPSS Inc, Chicago, Ill.)

growth in the cerebrospinal fluid. In the remaining patient, the autopsy results showed meningitis and cerebral microabscesses. In prosthetic valve IE due to S aureus, there were 12 patients with neurologic complications: in 6, the CT scan performed in the first 48 hours of hospitalization demonstrated brain hemorrhage, which was confirmed at necropsy in 2 patients, and in 3, the initial CT scan showed an ischemic infarct and hemorrhagic transformation was indicated clinically. Brain death supervened within the next 72 hours in all these patients. The remaining patient, who had a biological prosthesis and did not undergo anticoagulant therapy, had a mycotic aneurysm indicated by a CT scan. This patient died in 48 hours due to sepsis and multiorgan failure. Prothrombin time within the first 24 hours of the diagnosis of IE involving prosthetic valves in patients who subsequently developed neurologic complications ranged from 19% to 50% (during the period of the study international normalized ratio was not available in most patients in our institution). In all patients, heparin was substituted for oral anticoagulant therapy at the time of diagnosis.

No case of resistance to methicillin sodium resistance was observed during the study period. Therefore all patients, except 3 patients who were allergic to penicillin, received cloxacillin. The use of the drug was maintained for 6 weeks in the survivors and combined with gentamicin sulfate in the first 3 to 7 days. Surgical treatment was considered in all cases of prosthetic valve IE due to S aureus; however, only 6 of the 21 patients could undergo surgery. In 11, surgery was contraindicated because of active brain hemorrhage, which was the cause of death in all these patients; 2 patients died due to sepsis and multiorgan failure before surgery could be performed; and 2 patients refused to undergo surgery: both survived the acute phase of the infection but one underwent surgery 3 months later due to prosthetic valve dysfunction and the other was a 79-

Neurologic Complications, Mortality, and Causes of Death

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Native Valve IE (n = 35)</th>
<th>Prosthetic Valve IE (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke*</td>
<td>7 (20)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1 (3)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>4 (11)</td>
<td>1 (5)†</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>13 (37)</td>
<td>15 (71)‡</td>
</tr>
<tr>
<td>Causes of death§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system events</td>
<td>0 (0)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Postoperative†</td>
<td>5 (14)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Sepsis and multiorganic failure</td>
<td>6 (17)</td>
<td>1 (5)§</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Digestive hemorrhage</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* A hemorrhagic transformation was indicated by clinical criteria in 1 patient with native valve IE and in all patients with prosthetic valve IE.
† A patient had a simultaneous cerebral hemorrhage and 2 abscesses diagnosed from the results of a computed tomographic scan and necropsy.
‡ P = .02; odds ratio, 4.23 (95% confidence interval, 1.15-16.25).
§ P < .007 for the distribution of causes of death (stroke vs other).
||Postoperative indicates death during surgery or immediately after surgery.

Table
year-old woman who died of heart failure 6 months after discharge. In native valve IE due to S. aureus, surgery was performed in 16 patients who developed heart failure and/or embolic episodes, including 5 patients with a cerebral embolism and a CT scan showing ischemic stroke.

The overall mortality rate in left-sided IE due to S. aureus was 50%, while the rate for left-sided IE due to other microorganisms was 18% (P<.001; odds ratio [OR] 4.56; 95% confidence interval [CI], 2.45-8.59). In 13 patients (37%), mortality was due to native valve IE due to S. aureus and in 15 patients (71%), mortality was due to prosthetic valve IE due to S. aureus (P = .02; OR, 4.23; 95% CI, 1.15-16.25). The causes of death in left-sided IE due to S. aureus IE are shown in the Table. No patient in the native valve IE group died of cerebral damage, while 11 patients in the prosthetic valve IE group died of confirmed (6 patients) or clinically indicated (5 patients) brain hemorrhage. The difference in the distribution of the causes of death (stroke vs other) was highly significant (P<.007).

COMMENT

Embolic episodes and central nervous system involvement have been well described in IE due to S. aureus, and the results of our study agree with previous reports. The most common central nervous system involvement is ischemic stroke, and brain hemorrhage is reported to occur in 5% of patients with IE. The mechanisms of brain hemorrhage in IE have been related to ruptured mycotic aneurisms, hemorrhagic transformation of an ischemic infarction, and arterial rupture due to arteritis. Also, several authors described a tendency toward early brain hemorrhage in IE due to S. aureus during the bacteremic phase.

In our series, we found a difference in the clinical presentation of cerebral complications between native valve IE due to S. aureus and prosthetic valve IE due to S. aureus that had an important impact on outcome. Although 11 patients with native valve IE due to S. aureus had central nervous system involvement, brain hemorrhage occurred only in 1 and no patient died due to central nervous system damage. However, 11 patients with prosthetic valve IE due to S. aureus had clinical evidence of severe brain damage, leading to death in the first 72 hours. Brain hemorrhage was clinically indicated in all and could be confirmed by CT scans or autopsy results in 6.

All patients with prosthetic valve IE due to S. aureus with mechanical prostheses were undergoing oral anticoagulant therapy, while no patient with native valve IE due to S. aureus was undergoing such treatment. Therefore, it seems clinically plausible that anticoagulant therapy played a deleterious effect on the neurologic complications. According to the prothrombin times, these patients did not appear to have excessively depressed coagulation, which could have led by itself to brain hemorrhage.

The role of anticoagulant therapy in IE has been controversial. In patients with prosthetic valve IE, anticoagulant therapy is usually maintained unless embolic complications arise. A previous study on prognostic factors in prosthetic valve IE showed that anticoagulant therapy was an independent predictor of mortality in patients with IE caused by S. aureus. Our results also suggest that in left-sided IE due to S. aureus anticoagulant therapy is strongly correlated with death due to neurologic damage, which as a rule occurs early in the course of the disease. Although we studied a retrospective observational series, according to our data, it seems wise to suggest that as soon as the clinical diagnosis of IE due to S. aureus is indicated, even before an ischemic stroke is diagnosed, anticoagulant therapy should be immediately stopped until the septic phase of the disease, which usually lasts a few days, is overcome. Once the sepsis is controlled, a good therapeutic strategy is to resume anticoagulant therapy with heparin until the decision is made regarding surgery. As recently reported, surgery should probably be performed in all patients with prosthetic valve IE due to S. aureus. In view of our results, it seems likely that the risk of emboli because of delayed anticoagulant therapy during such a short period will be less than the risk of inducing fatal cerebral hemorrhage. The recommendation to stop anticoagulant therapy seems to be even stronger in those patients who have developed features of ischemic stroke, in whom the risk of hemorrhagic transformation is high, and in whom such a measure might modify a poor prognosis.

Accepted for publication June 18, 1998

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REFERENCES