Prevention of Thromboembolism Using Aspirin after Mitral Valve Replacement with Porcine Bioprosthesis

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ABSTRACT **The thromboembolic rate of 768 patients who were treated only with aspirin after mitral valve replacement or mitral plus aortic valve replacement with porcine bioprostheses was evaluated. We analyzed the thromboembolic rate for the whole series and for subgroups of patients categorized by atrial fibrillation, giant left atrium, left atrial thrombosis, and dosage of aspirin (1 gm daily or 0.5 gm every 48 hours). The total embolic rate was 1.4% (11/768). No patient in sinus rhythm had an embolic event. The embolic rate for patients in atrial fibrillation was 1.9% (11/583). There were no embolic events in 31 patients with a giant atrium. An embolic event occurred in 1 of 42 patients with atrial thrombosis (2.4%). Patients treated with 1 gm of aspirin daily had a 3% embolic rate (9/295) while the incidence was 0.4% (2/473) in those treated with 0.5 gm every 48 hours ($p < 0.01$).**

Administration of aspirin after mitral valve replacement with a bioprosthesis is a very effective treatment for prevention of thromboembolism. In our experience, this treatment provides protection equal to or better than that offered by oral anticoagulants for patients in atrial fibrillation as well as for patients with a giant atrium or atrial thrombosis at operation. The dosage and timing of aspirin administration may markedly affect the result of this type of treatment. Oral anticoagulation with coumarin derivatives may not be appropriate after mitral valve replacement with a bioprosthesis, and platelet antiaggregates should be used for this purpose in the future.

Replacement of a cardiac valve with a mechanical prosthesis carries a permanent risk of thromboembolism. Long-term oral anticoagulation is the accepted treatment for prevention of this complication. Tissue valves were introduced into clinical use because they are less thrombogenic, but certain clinical situations have been shown to carry an increased risk of thromboembolism even when bioprostheses are implanted. Mitral valve replacement, atrial fibrillation, a giant left atrium, and thrombus in the left atrium are known to be highly thrombogenic. In series previously reported in the literature, the choice of a bioprosthetic mitral valve under such circumstances was followed by the use of long-term anticoagulation in a high percentage of patients.

Since 1975, we have been giving patients platelet antiaggregates after mitral valve replacement with a porcine bioprosthesis. Since 1979, all patients operated on in our department have received only aspirin for prevention of thromboembolism. This article reports our experience with patients who had isolated mitral or double-valve replacement with porcine bioprostheses and were treated only with aspirin.

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Patients and Methods

From April, 1975, to April, 1982, 768 patients at our institution had isolated mitral valve replacement or aortic plus mitral valve replacement with bioprostheses and were treated solely with aspirin for prevention of postoperative thromboembolism. The ages of these patients ranged from 6 to 78 years with a mean age of 44.2 years. Of the 768 patients, 452 were women.

Hancock valves were implanted in 128 patients and Carpentier-Edwards valves in 640 patients. Isolated mitral valve replacement was performed 435 times and double-valve replacement (aortic and mitral) 333 times. Associated procedures included 92 tricuspid annuloplasties, 29 coronary artery bypass graft procedures, 16 repairs of congenital defects, and 13 miscellaneous repairs. Forty-two patients required extensive left atrial thrombectomy because of thrombosis covering most of the left atrial wall. In each patient, the left atrial appendage was ligated during the procedure.

Follow-up was accomplished by personal examination every 3 to 6 months. The follow-up period ranged from 3 months to 7 years. Mean follow-up was 32 months, and total follow-up was 2,048 years. Twenty-six patients lost to follow-up after the first year were included in the final follow-up examination.

The cause of cardiac valve disease was rheumatic in 706 patients and nonrheumatic in 62 (coronary disease, myxoid degeneration, and bacterial endocarditis).

Platelet Antiaggregation

From April, 1975, to October, 1979, each patient received 1 gm of aspirin daily, starting on the second postoperative day. Since October, 1979, 0.5 gm of aspirin has been given, starting on the first postoperative day. Aspirin was maintained as a long-term treatment in all patients.

Definitions and Statistical Analysis

For our study, we defined *thromboembolism* as any event characterized by suggestion or evidence of acute arterial

obstruction in any area of the arterial tree. Embolism was considered major when death, permanent damage, or operation followed. Patients with confirmed bacterial endocarditis were excluded. We used the term *early thromboembolism* to describe episodes occurring within the first 3 postoperative months. We considered any bleeding, whether or not a predisposing disease was present, to be a *hemorrhagic event*. A *giant atrium* was defined as any left atrium measuring more than 7 cm by echocardiography. We used the term *atrial thrombosis* to denote the presence at operation of a left atrial thrombus covering most or all of the atrial wall.

Thromboembolism was studied for the whole group and for the following variables: (1) atrial rhythm, (2) giant atrium, (3) atrial thrombosis, and (4) dosage of aspirin. Treatment groups were compared by a nonparametric analysis of variance and standard chi-square test for independence in a two-way table.

Results

Eleven of the 768 patients had thromboembolic events (1.4%). There were no deaths due to thromboembolism. Nine embolic episodes occurred early and 2 late in the postoperative period; 2 were considered major. No patient in regular sinus rhythm had thromboembolism.

Table 1. Data on Valve Replacement Patients Receiving Postoperative Treatment with Aspirin

Type of Valve Replacement and Atrial Rhythm	No. of Patients	No. of Embolisms	%	Incidence of Embolism[a]
MVR	435	7	1.6	0.6
Sinus rhythm	81	0	0	0
Atrial fibrillation	354	7	2.0	0.7
MVR + AVR	333	4	1.2	0.4
Sinus rhythm	104	0	0	0
Atrial fibrillation	229	4	1.7	0.6
Total	768	11	1.4	0.5

[a]Incidence is number of thromboembolic events per 100 patients per year.

MVR = mitral valve replacement; AVR = aortic valve replacement.

Embolic episodes occurred in 11 of 583 patients in atrial fibrillation (1.9%). Of 354 patients with isolated mitral valve replacement and atrial fibrillation, 7 (2%) had embolic episodes, while 4 of 229 patients (1.7%) with double-valve replacement and atrial fibrillation had embolic episodes (Table 1).

No episodes occurred in 31 patients with a giant left atrium. The embolic rate in patients with intraoperative left atrial thrombosis was 2.4% (1/42). Nine embolic episodes occurred in patients treated with 1 gm of aspirin daily (3%, 9/295), while only 2 occurred in the group of 473 treated with 0.5 gm every 48 hours (0.4%).

Comparison of patients in atrial fibrillation treated with the two different regimens of aspirin dosage showed the lower dosage of the drug to be significantly more effective ($p < 0.01$) (Table 2).

In 4 of the 768 patients, gastrointestinal bleeding developed (0.5%). One of these patients required blood transfusions, and 1 suffered a femoral embolism 14 days after aspirin withdrawal. There were no deaths due to bleeding.

Comment

After more than 10 years of widespread use of glutaraldehyde-preserved porcine bioprostheses, questions about their durability, the physiopathology of biological tissue degeneration, and the optimal drug regimen for prevention of thromboembolism remain to be answered. Bioprostheses were accepted in clinical use mainly because of their low incidence of thrombogenicity [1, 2]. We observed that mitral valve replacement by a bioprosthesis had a high rate of thromboembolism during the first postoperative months when no anticoagulation was given [3]. Late thromboembolism, however, was very rare and almost unknown in patients in sinus rhythm. Because this peculiar pattern of embolization was so different from the one found in patients with mechanical prostheses, we assumed in 1975 that thromboembolic events in the early period were caused by the uncovered sewing ring of the valve or by atrial injury produced during the operation, and that the biological tissue itself was nonthrombogenic.

Table 2. Aspirin Dosage and Incidence of Peripheral Embolism for Valve Replacement Patients in Atrial Fibrillation

Type of Valve Replacement and Aspirin Dosage	No. of Patients	No. of Embolisms	%	Incidence of Embolism[a]	
MVR					
1 gm of aspirin daily	135	6	4.4	1.3	$p < 0.01$
0.5 gm of aspirin every 48 hr	219	1	0.5	0.3	
MVR + AVR					
1 gm of aspirin daily	86	3	3.5	1.1	NS
0.5 gm of aspirin every 48 hr	143	1	0.7	0.5	
Total for patients given 1 gm of aspirin daily	221	9	4.0	1.2	
Total for patients given 0.5 gm every 48 hr	362	2	0.5	0.4	

[a]Incidence is number of events per 100 patients per year.

MVR = mitral valve replacement; AVR = aortic valve replacement; NS = not significant.

Previous studies have partially confirmed this hypothesis. Thiene and associates [4] have reported that early thrombus formation after mitral valve replacement with a bioprosthesis is located either in the host-tissue interface or in the left atrial wall. Ben-Schachar and colleagues [5] have also observed that thrombi occurring after mitral valve replacement are usually located on the septum or in the posterior left atrial wall.

Administration of anti–vitamin K derivatives has been unavoidable for patients with mechanical valve prostheses [6, 7, 8]. This treatment should be continued for life, because thromboembolism that occurs in the presence of a mechanical valve is mainly related to the thrombogenic properties of the valve itself. Although a low incidence of bleeding has been reported for many series, some authors have reported a hemorrhage rate as high as 15% [9]. Thromboembolism and bleeding in patients treated with coumarin derivatives is an ever-present threat because the efficacy of these drugs is influenced by many factors.

This traditional need for oral anticoagulation after valve replacement has caused surgeons to assume that patients with bioprostheses also have to be anticoagulated. Different regimens of oral anticoagulation have been used for this purpose [10–13]. Two recent articles, however, have shown that aspirin administration may benefit patients with cardiac bioprostheses as well as oral anticoagulation can and with less risk [14, 15].

The data collected for this report show the low incidence of thromboembolism that can be achieved by the use of aspirin alone after isolated mitral or double-valve replacement with porcine bioprostheses. The embolic rate of 1.4% (11/768) for the entire series is as good as any obtained in other series with oral anticoagulation [10–13]. By the same token, the incidence of thromboembolism in patients with atrial fibrillation who had isolated mitral valve replacement (2%; 7/354) or double-valve replacement (1.7%; 4/229) is as low as or lower than any reported for bioprosthetic valve replacement [10–13, 16–18]. Patients with a giant left atrium or with left atrial thrombosis had the same incidence of peripheral embolism as did patients in general. Our rates of thromboembolism with aspirin and bioprostheses are very similar to those reported after plastic repair of the mitral valve [19–21].

Two important aspects of aspirin administration should be emphasized. The dosage of aspirin has a statistically significant impact on the incidence of peripheral embolism. Patients given 0.5 gm of aspirin every 48 hours showed a lesser incidence of thromboembolism than those who received 1 gm of aspirin daily. The timing of antiplatelet treatment is also important. The hypothesis that operative events (intraoperative atrial injury or uncovered Dacron) are the main causes of early thromboembolism infers the advisability of early administration of aspirin. Since 1979, we have given the first dose of aspirin as soon as the patient could tolerate a liquid diet, usually within the first postoperative day.

Patients in normal sinus rhythm did not have a single episode of peripheral embolism. This fact should lead us to assume that bioprosthetic tissue may carry such a low risk of thrombogenicity that it can be controlled with platelet antiaggregates. Late embolic episodes (there were only 2 in our series) may be caused by late changes in biological tissue [4], impaired atrial function [22], or worn-out nonbiological bioprosthetic tissue [23]. For these reasons, and because some patients in normal sinus rhythm may later go into atrial fibrillation, we recommend a life-long regimen of aspirin for these patients.

Only 4 patients in our series had bleeding complications. This very small risk, as well as the protection obtained against thromboembolism for every type of patient who required a mitral bioprosthesis, has led us to adopt the policy of not using coumarin after cardiac valve replacement with a bioprosthesis. Since October, 1979, no patient in our department has been treated with anti–vitamin K derivatives for this purpose.

We firmly believe that patients with any type of mechanical valve prosthesis should be treated forever with anti–vitamin K derivatives [6–24]. Platelet antiaggregates should not be used alone for prevention of postoperative thromboembolism after implantation of mechanical cardiac valves.

Our experience with bioprosthetic valve replacement, however, indicates that platelet antiaggregation is more effective than oral anticoagulation for this type of prosthesis. It may be that bioprostheses are not very thrombogenic once the nonbiological part of the valve is covered by host tissue. Mechanical prostheses, on the other hand, are always thrombogenic. Aspirin seems to prevent left atrial thromboembolism during the early postoperative period by hindering thrombus formation in the left atrial wall, caused by operative injury, and in the uncovered sewing ring. In the late postoperative period, aspirin reduces the possibility of thrombus formation in the malfunctioning left atrium (atrial fibrillation).

The lower mean age of our patients (44 years) compared with that in most American studies (55 years or older) may suggest that some vascular obstructive episodes included as embolisms in these other reports may have a different cause (thrombosis or hemorrhage). Another possibility is that patients orally anticoagulated may have temporary periods of global hypercoagulability even with prothrombin times in the "therapeutic" range, while platelet antiaggregation produces a steadier state of hypocoagulability.

This report confirms the thesis reported by Hill and co-workers [14] and Nuñez and associates [15] that warfarin anticoagulation may not be necessary after porcine bioprosthetic replacement of the mitral valve. Prevention of postoperative thromboembolism after mitral valve replacement with a bioprosthesis should probably be looked at from a different perspective than prevention of thromboembolism after mechanical valve replacement. Although the final objective is to diminish the rate of thromboembolism, the origin of thrombus formation and the method for avoiding this formation may differ

according to type of prosthesis. From an empirical point of view, aspirin in an appropriate dosage may be substituted for oral anticoagulation when a bioprosthesis is used.

Editor's Note

This report is essentially a descriptive study of the postoperative therapy of patients who underwent valve replacement with a bioprosthesis. It must be pointed out that there is no internal control group. The incidence of postoperative thromboembolism is low, but there is no comparison that allows the conclusion that aspirin is an effective drug for prevention of thromboembolism.

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