Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial


ABSTRACT In a prospective, randomized, parallel study, two regimens of platelet-suppressant therapy (PST) — dipyridamole-aspirin and pentoxifylline-aspirin — were compared with standard oral anticoagulation with warfarin in the prevention of prosthetic heart valve thromboembolism. In the entire group of 254 patients followed for 395.6 patient-years, the thromboembolic rate was significantly less in the warfarin group (warfarin vs dipyridamole-aspirin, p < .005; warfarin vs pentoxifylline-aspirin, p < .05). Subgroup analysis disclosed that, in patients with isolated mitral valve replacement, warfarin was superior to both of the PSTs with respect to the prevention of thromboembolism (warfarin vs dipyridamole-aspirin, p = .005; warfarin vs pentoxifylline-aspirin, p < .05). Furthermore, a significant number of our patients could not tolerate the antiplatelet agents. However, in the rare situation in which repeated significant bleeding occurs despite careful adjustment of the dosage of warfarin, PST may be an acceptable alternate method of thromboembolism prophylaxis.


WHEN THE EFFECT of anticoagulant is maintained within a therapeutic range it significantly reduces, but does not eliminate, the risk of thromboembolism in patients with prosthetic heart valves. However, adequate anticoagulation at all times is difficult to achieve, and it carries a definite risk of its own. In clinical practice, whenever the use of oral anticoagulation is complicated, e.g., in children with prosthetic heart valves or when adequate facilities for careful anticoagulation are not available, antiplatelet agents have been used as the alternatives. It would be advantageous to patients with prosthetic heart valves if platelet-suppressant therapy (PST) could be used in place of oral anticoagulation. We undertook a prospective, randomized, parallel study to evaluate the efficacy of PST for the prevention of thromboembolism in patients with mechanical prosthetic heart valves. Anticoagulation with warfarin was used as the control. The regimens of antiplatelet agents used in the present study were derived from our previous study on platelet survival among patients with mechanical prosthetic heart valves. The present report is an analysis of the relevant data from the prospective trial.

Methods

From January 1979 to January 1984, patients with mechanical prosthetic heart valves (models 1260 and 6120 Starr-Edwards and standard Björk-Shiley) discharged to our valvular clinic were interviewed. The risks and benefits of anticoagulation, PST, and the proposed drug trial were explained to them in detail. Informed consent was obtained from those who agreed to participate in the prospective study. After 6 months of warfarin therapy, they were assigned to one of the three treatment groups (warfarin, dipyridamole-aspirin, and pentoxifylline-aspirin) by means of random-numbered tables and irrespective of the location and type of the prosthesis they had received. It was thought that 6 months would be required for the sewing ring of the prosthesis to become endothelialized.

Patients in the warfarin group continued to receive the drug in doses that maintained their prothrombin times within the therapeutic range (1.8 ≤ prothrombin time/control ≤ 2.5). The dipyridamole-aspirin group received 75 mg dipyridamole twice daily and slow-releasing aspirin, 650 mg once daily; since January 1982, they have received Persantin Plus (dipyridamole 75 mg + aspirin 330 mg), one tablet three times daily. The change was made for the convenience of patients and the dispenser. The

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pentoxifylline-aspirin group received 400 mg pentoxifylline twice daily and slow-releasing aspirin, 650 mg daily. Dosing with warfarin was discontinued in the two groups of patients who had been assigned to receive PSTs. All participants were instructed not to take any other medications, including herbal medicines, on their own.

Participants were evaluated at monthly intervals or earlier when required. At each visit, compliance with all regimens was assessed by counting of tablets and in those receiving warfarin prothrombin times were also measured. All participants were also checked for significant bleeding complications, i.e., bleeding necessitating hospitalization.

Follow-up end points included the following: (1) Thromboembolism, defined as an embolic episode resulting in transient or permanent neurologic deficit with focal motor weakness or visual deficit or loss of pulses in an extremity and of sudden onset and unexplained by other causes. Cerebral bleeding was excluded at autopsy or by a computerized tomographic scan. Thromboembolism was verified either at autopsy or reoperation. A coronary embolus was diagnosed only when the coronary arteries were known to be normal or when a myocardial infarction occurred in a patient younger than 40 years of age without apparent risk factors other than the presence of the prosthetic valve. (2) Drug intolerance, i.e., appearance of drug-related symptoms that prevented continuation of therapy with the drug.

When a thromboembolic episode occurred in a patient in the warfarin group, he or she was given a larger dose of warfarin if the prothrombin time was below the therapeutic range; when the prothrombin time was within the therapeutic range dipyridamole (400 mg daily) was added. Patients on PST who had an episode of thromboembolism or required discontinuation therapy with antiplatelet drugs were put back on warfarin. Data on the subsequent clinical courses of these patients, both in the warfarin and the PST groups, were not included in the analysis. Statistical analysis was by the corrected chi-square test, the unpaired Student’s t test, and the generalized Wilcoxon comparison of incident-free rates determined by the Kaplan-Meier product-limit actuarial method.7 Statistical significance was assumed at the 5% level.

Results

Of the 254 patients randomly assigned to drug therapy, 251 received the medications assigned to them. Two patients withdrew consent after randomization and one patient was withdrawn because she became pregnant before PST was to commence. Data from these three patients were included in the final analysis. The comparability in clinical characteristics of the 254 patients in the three randomized treatment groups is shown in table 1.

Follow-up was complete. The mean follow-up periods and overall results are listed in table 2. The manifestations and distribution of the thromboembolic and bleeding episodes are listed in table 3. During the study period, six patients died of causes unrelated to the prosthesis or thromboembolic prophylactic therapy. Death was due to congestive heart failure in two patients, arrhythmia in one patient, infective endocarditis in one patient, ruptured aortic aneurysm in one patient, and carcinoma of the ovary in one patient.

Adequacy of anticoagulation. There were 3132 prothrombin times and corresponding control values tabulated during the follow-up of patients in the warfarin group. The prothrombin times of approximately 50% of the patients were within, those of 30% were above, and those of 20% were below the therapeutic range (1.8 ≤ prothrombin time/control ≤ 2.5).

Incidence of thromboembolism

Warfarin group. There were four thromboembolic events (2.2 per 100 patient-years), and one patient died following coronary embolism.

Dipyridamole-aspirin groups. Eleven patients developed thromboembolism (8.6 per 100 patient-years), and two patients died. Coronary embolism was the cause of death in one, and a thromboembolism was the cause in the other patient.

Pentoxifylline-aspirin group. Eight thromboembolic events occurred (7.9 per 100 patient-years). All eight patients survived the thromboembolic episode.

<table>
<thead>
<tr>
<th>TABLE 1 Clinical characteristics of the patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (p = .20)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Prior thromboembolism (p = .61)</td>
</tr>
<tr>
<td>Left atrial enlargement (p = .14)</td>
</tr>
<tr>
<td>LA thrombus at operation (p = .62)</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation (p = .36)</td>
</tr>
<tr>
<td>Valve type (p = .20)</td>
</tr>
<tr>
<td>Starr-Edwards</td>
</tr>
<tr>
<td>Björk-Shiley</td>
</tr>
<tr>
<td>Valve position (p = .10)</td>
</tr>
<tr>
<td>Mitral</td>
</tr>
<tr>
<td>Aortic</td>
</tr>
<tr>
<td>Both mitral and aortic</td>
</tr>
<tr>
<td>LA = left atrial.</td>
</tr>
</tbody>
</table>

(*) Determined with M mode echocardiography (>5 mm in size).
TABLE 2

Overall results in the three treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Dipyridamole-aspirin</th>
<th>Pentoxifylline-aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (n = 97)</td>
<td>(n = 81)</td>
<td>(n = 76)</td>
</tr>
<tr>
<td>mean FU period</td>
<td>24.4 mo</td>
<td>18.0 mo</td>
</tr>
</tbody>
</table>

Treatment “failure” (n)
- Thromboembolism (death) 4 (4.1%) 11 (13.6%) 8 (10.5%)
- Drug intolerance 0 22 (27.2%) 24 (31.6%)
- Bleeding 5 (5.2%) 0 1

Treatment “success” (patients without emboli, on drugs; n)
- Death not related to treatment (n) 4 0 2

FU = follow-up.

Episodes of bleeding. There were six episodes of bleeding. All patients survived. Five episodes occurred in the warfarin group and one occurred in the pentoxifylline-aspirin group. Of the five patients who bled in the warfarin group, four had markedly prolonged prothrombin times. One patient in the pentoxifylline-aspirin group developed spontaneous hemo-

TABLE 3

Manifestations of thromboembolic and bleeding episodes

<table>
<thead>
<tr>
<th></th>
<th>Dipyridamole-aspirin</th>
<th>Pentoxifylline-aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (n = 97)</td>
<td>(n = 81)</td>
<td>(n = 76)</td>
</tr>
</tbody>
</table>
| Thromboembolic episodes (n)
  - Hemiparesis/hemiplegia with residue 1 2 1
  - Transient hemiparesis 1 6 5
  - Thrombosed prosthesis 0 2 1
  - Acute myocardial infarction 1 1 1
  - Peripheral arterial embolism 1 0 0

Bleeding episodes (n)
- Gum bleeding 1 0 0
- Hematuria 1 0 0
- Hemarthrosis 1 0 0
- Hemoperitoneum 0 0 1
- Infracerebral hematoma 1 0 0
- Menorrhagia 1 0 0

peritoneum that was diagnosed at laparotomy. Both the cause and source of bleeding were obscured.

Drug intolerance. Antiplatelet therapy was discontinued in 46 patients (22 of 81 [27.2%] in the dipyridamole-aspirin group and 24 of 76 [31.6%] in the pentoxifylline-aspirin group). With the exception of one patient who developed a skin rash, intolerable gastrointestinal upset was the reason for cessation of therapy.

Comparison between treatment groups. The actuarial curves depicting the thromboembolic-free intervals in the three groups of patients are shown in figure 1. There was a significant difference between the warfarin and each of the 2 PST groups (warfarin vs dipyridamole-aspirin, p < .005; warfarin vs pentoxifylline-aspirin, p < .05). Results of subgroup analysis according to the position of the valve are summarized in table 4. Among the patients who had undergone single mitral valve replacement (figure 2), there was a significant difference in the incidence of thromboembolism between those in the warfarin and those in each of the two PST groups (warfarin vs dipyridamole-aspirin, p = .005; warfarin vs pentoxifylline-aspirin, p < .05). Given the small number of patients in the other two subgroups (aortic and double) no significant difference was found in the thromboembolic-free intervals in the three treatment groups.

When significant bleeding and thromboembolism were considered together as undesirable events, the difference in the event-free intervals between the warfarin and dipyridamole-aspirin groups was significant (p < .05), but no such difference was observed between the warfarin and pentoxifylline-aspirin groups.
TABLE 4
Subgroup analysis according to valve positions

<table>
<thead>
<tr>
<th>Valve Position</th>
<th>TE (per 100 patient-years)</th>
<th>p value (comparison of TE-free periods)</th>
<th>p value (comparison of event-free periods)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W</td>
<td>D-A</td>
<td>P-A</td>
</tr>
<tr>
<td>All valves</td>
<td>4/97</td>
<td>11/81</td>
<td>8/76</td>
</tr>
<tr>
<td>(2.2)</td>
<td>(9.8)</td>
<td>(7.9)</td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>2/62</td>
<td>9/54</td>
<td>6/43</td>
</tr>
<tr>
<td>(1.9)</td>
<td>(12.4)</td>
<td>(11.5)</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>1/14</td>
<td>1/15</td>
<td>2/21</td>
</tr>
<tr>
<td>(3.6)</td>
<td>(3.8)</td>
<td>(5.6)</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>1/21</td>
<td>1/12</td>
<td>0/12</td>
</tr>
<tr>
<td>(2.1)</td>
<td>(7.4)</td>
<td>(0)</td>
<td></td>
</tr>
</tbody>
</table>

TE = thromboembolism; W = warfarin; D-A = dipyridamole-aspirin; P-A = pentoxifylline-aspirin.

nor among the treatment groups when they were further subdivided according to the position of the valves they had received (table 4).

We did not find any significant difference in the thromboembolic or event-free rates nor the percentages of “successful treatment” (table 2) for the two PST groups. Within each treatment group, there was no demonstrable difference in the thromboembolic rate between patients with the two types of prosthesis.

Discussion

Prophylaxis against thromboembolism is unavoidable in the majority of our patients after prosthetic heart valve replacement because they prefer the more durable mechanical valves, and many of them have a large left atrium and are in atrial fibrillation. Because of the lack of resources and the common occurrence of self-administration of herbal medicines that may interact with oral anticoagulants in our patients, we have had difficulties with running a conventional anticoagulation clinic. We therefore felt justified in conducting the present trial in a search for an acceptable substitute for conventional anticoagulant therapy.

As mentioned before, the two regimens of PST were derived from our previous study on platelet survival in patients with mechanical prosthetic heart valves. The study demonstrated that 100 mg dipyridamole plus 1200 mg aspirin daily and 600 mg pentoxifylline plus 1200 mg aspirin daily normalized platelet survival. The minor modifications that were made in dosages for use in the present study were made to attempt to improve patient compliance and allow use of slow-releasing preparations.

The present study conclusively demonstrated that our two regimens of PST were inferior to warfarin therapy in the prevention of thromboembolism among patients with mechanical mitral prostheses. Although there were no significant differences in the incidence of thromboembolism between the treatment groups in patients with aortic or double valve replacement, we hesitate to conclude that our regimens of PST can replace oral anticoagulation in these subsets of patients because the number of patients in each of these subgroups was small. Since analysis of the event-free intervals demonstrated no difference among the subgroups (table 4), PST may be of value in the rare situation in which repeated significant bleeding occurs despite careful adjustment of dosages of warfarin.

Side effects of use of antiplatelet agents that led to discontinuation of therapy were common in previous studies of PST. However, the incidence of drug intol-
erance we found (dipyridamole-aspirin, 27.2%; pentoxifylline-aspirin, 31.6%) was higher than that observed in other studies in which similar drugs were used (7.5% to 17.6%). The most significant symptom among our patients was intolerable gastrointestinal upset. In that the drugs and dosages used were comparable to those reported in previous studies, these reactions may perhaps be attributable to increased sensitivity in the indigenous population studied.

Our results show that PST by itself, when given arbitrarily, is not as effective as conventional anticoagulation in the prevention of thromboembolism in an unselected group of patients with mechanical prosthetic heart valves. On the other hand, it is generally accepted that the addition of dipyridamole to a regimen of anticoagulant reduces the incidence of prosthetic valve-related thromboembolism. Thus, the exact role of antiplatelet drugs in prophylaxis of prosthetic valve thromboembolism is still largely unknown. This will remain undefined until the effective agents, the optimal dosage to be used, and a laboratory test of platelet reactivity that correlates with thromboembolism are discovered.

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