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Anti-platelet therapy in graft thrombosis: Results of a prospective, randomized, double-blind study

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Anti-platelet therapy in graft thrombosis: Results of a prospective, randomized, double-blind study. Hemodialysis (HD) vascular access thrombosis remains a major cause of morbidity, accounting for 17.4% of all HD patient hospital admissions in 1986. We initiated this prospective, randomized, double-blind, placebo-controlled, parallel group study to examine if dipyridamole and/or aspirin decreased the rate of thrombosis of expanded polytetrafluoroethylene (ePTFE) grafts in HD patients. Two patient groups were studied: Type I—with a new ePTFE graft; and Type II—with thrombectomy and/or revision of a previously placed ePTFE graft. One hundred and seven patients were followed for 18 months or until the first thrombotic episode. Actuarial analysis of Type I patients showed cumulative thrombosis rates (mean ± SEM) of 21 ± 9% on dipyridamole alone, compared with 25 ± 11% on dipyridamole and aspirin combination, 42 ± 13% on placebo, and 80 ± 12% on aspirin alone. The relative risk of thrombosis with dipyridamole was 0.35 ($P = 0.02$) and that for aspirin was 1.99 ($P = 0.18$). In Type II patients, the rate of thrombosis was high in all study drug and placebo groups (overall 78% thrombosis) and actuarial analysis was not carried out because of the small number of patients enrolled. We conclude that dipyridamole is beneficial in patients with new ePTFE grafts and that aspirin does not improve the risk of thrombosis in ePTFE grafts. Neither dipyridamole nor aspirin has any beneficial effect in patients with prior thrombosis of ePTFE grafts.

Complications of the vascular access, particularly stenosis and thrombosis, continue to remain the Achilles' heel of hemodialysis (HD) therapy and lead to extensive morbidity in HD patients. In 1986, end-stage renal disease (ESRD) patients had approximately 30,000 vascular access related hospital admissions (with a median duration of 7 days each) constituting 17.4% of all hospital stays in this population [1]. In addition to its impact on patient morbidity, the annual cost for placement and maintenance of vascular access is estimated to be approximately $500 million [2].

The autologous brachio-cephalic (Brescia-Cimino) fistula remains the access of choice, since its patency and rate of infection are superior to those made of exogenous material once early failures are excluded [3]. However, polytetrafluroethylene (PTFE) arteriovenous grafts are used with increasing frequency. In 1990, 83% of vascular accesses placed in Medicare-dependent ESRD patients were PTFE grafts [4]. This is attributed to an increased proportion of elderly patients, female gender, diabetic patients, and patients with multiple prior indwelling intravenous catheters or prior failure of autologous fistulae, all of whom tend to have poor vasculature that preclude the formation of autologous fistulae.

Hemodialysis vascular access thrombosis can occasionally be attributed to mechanical factors, and at times to a hypercoagulable state [5]; however, neointimal hyperplasia and stenosis at the venous anastomosis appear to be the most common factors associated with thrombosis [6–8]. Platelet activation has been proposed to play an important role in the development of neointimal hyperplasia, and several studies have been performed to assess the efficacy of anti-platelet drugs in the prolongation of patency of vascular grafts. Anti-platelet therapy has been reported to decrease thrombosis in external silastic cannula such as the Scribner shunts used for dialysis vascular access [9, 10], and data from animal studies have demonstrated their efficacy in large vessel vascular grafts [11–13]. The combination of aspirin and dipyridamole was also shown to be effective in human femorodistal PTFE grafts [14]. However, to our knowledge the long-term efficacy of anti-platelet therapy in the prevention of thrombosis of new or revised PTFE grafts in chronic HD patients has not been reported.

This prospective, randomized, double-blind, placebo-controlled, parallel group study was undertaken to examine if dipyridamole (PERSANTINE®) and/or aspirin decreased the rate of thrombosis of prosthetic arteriovenous expanded PTFE (ePTFE) grafts in patients on chronic HD.

Methods

Patients

The study was designed to investigate the effectiveness of anti-platelet therapy in two populations of patients: (a) Type I: Patients who required a new arteriovenous ePTFE graft for chronic HD. These included patients who were close to initiation of chronic HD, as well as patients who were on chronic HD but required placement of a new ePTFE graft at a different site. (b) Type II: Patients on chronic HD who already had an arteriovenous ePTFE graft but who developed graft thrombosis and required a thrombectomy and/or revision by interposition of a new ePTFE segment.

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Note that once patients participated in the study as either Type I or Type II, they were not eligible for further participation, that is, each patient was entered only once. There was no restriction on participation because of age, gender, diagnosis or prognosis.

Prior to enrollment, patients underwent a complete history and physical examination. Baseline laboratory investigations included a complete blood count, fasting SMA-20 and urinalysis (if available). Criteria for exclusion from the study were: uncontrolled hypertension (defined as a sitting diastolic blood pressure greater than 110 mm Hg), history of active peptic ulcer disease, hemophilia, von Willebrand's disease or other bleeding disorders, patients with neoplastic disorders and hypersensitivity to aspirin or dipyridamole.

Treatment protocols

Patients were randomly assigned to one of four drug regimens:

(1) Dipyridamole 75 mg three times a day (tid) with "aspirin" placebo once a day (qd);
(2) "Dipyridamole" placebo tid with aspirin 325 mg qd;
(3) Dipyridamole 75 mg tablet tid with aspirin 325 mg qd; or
(4) "Dipyridamole" placebo tid with "aspirin" placebo qd.

Placebo drugs looked identical to actual drugs and were similarly packaged. Neither patient nor investigator could determine the specific treatment protocol assigned to the patient. Randomization was done using a predetermined schedule. Aspirin or its matching placebo was taken with meals and during the initial daily dose of dipyridamole or "dipyridamole" placebo. Study medications were generally initiated one to two days prior to insertion of a new ePTFE graft or its thrombectomy, or within one day following the surgical procedure. Because of this requirement, and because thrombectomies of pre-existing grafts were generally performed in an outpatient setting, there were more Type I patients enrolled in the study than Type II patients.

Concomitant therapy

There was no attempt to change any parameters of dialysis prescription, including heparin dosage. Aspirin-containing medications, sulfinpyrazone, prostaglandin inhibitor drugs (indomethacin, ibuprofen, phenylbutazone, oxyphenylbutazone, naproxen, fenoprofen, tolmetin, and zomepirac), clofibrate, coumarins, theophylline, caffeine-containing medications, and colchicine were not prescribed during the study. Occasional use of coffee was allowed. None of the patients received erythropoietin (EPO) during the study period (1982 to 1988) as the drug was not available for general use in that time interval.

Follow-up

The primary endpoint of the study was thrombosis of the ePTFE graft. Thrombosis was detected by the lack of blood flow by palpation and auscultation or the presence of thrombus detected during introduction of the dialysis needle into the graft. Patients were evaluated by an investigator every two months for 18 months or until graft thrombosis, whichever occurred earlier. At the conclusion of the observation period (18 months or at the time of graft thrombosis), physical examination and laboratory tests were repeated. Adverse reactions to the drugs were recorded throughout the study. Compliance was determined by pill count, and by determining the level of thromboxane B_2 in aliquots of platelet-rich plasma (as a marker of aspirin intake).

Statistics

The primary null hypothesis of the study was that dipyridamole has no effect on graft thrombosis. Thrombosis rates were determined by both crude and actuarial rates. Crude thrombosis rates were determined for each arm of the study by calculating the proportion of patients with thrombosis at the end of the study period; these rates were then analyzed with Chi-square test. Although crude rates serve to introduce the results in simple terms, they fail to account for the time-to-observed event and for early withdrawals. We therefore used actuarial analysis for each treatment group as the primary analysis to determine the proportion of failed grafts as well as differences in rates of thrombosis between study drugs. In the actuarial analysis, observations on patients without thrombosis were considered to be independently censored at the last completed visit, and are therefore grouped into 60-day intervals corresponding to the planned time between patient visits.

The specific actuarial analysis used for testing the null hypothesis was the Cox proportional hazards model, with terms for dipyridamole and aspirin and stratified by type of patient, that is, Type I or Type II. The initial application of the Cox model indicated statistically significant treatment-by-type interaction, suggesting that Type I patients differed in outcome from Type II patients. We, therefore, carried out the Cox analysis separately for Type I patients. Because this analysis was considered to be a subgroup analysis with repeated testing, calculated P values for each group of patients were multiplied by 2 in order to adjust for the repeated testing. There were too few Type II patients to warrant a separate analysis of their data. Therefore, the results of the study will emphasize the outcome of Type I patients.

Results are expressed as mean ± SEM unless otherwise indicated. $P < 0.05$ was considered statistically significant.

Results

Outcome analysis

Patients were enrolled from April 1982 to February 1988. There were 108 patients (63 females and 45 males) admitted to the study. The mean age was 54.4 years (range: 19 to 84 years), the mean weight was 157.2 pounds (range: 70 to 255 pounds), and the mean height was 65.8 inches (range: 55 to 73 inches). Seventy-four patients were white, 32 were black, and the remaining two were hispanic. Demographic and baseline characteristics summarized by treatment type are given in Table 1.

Of the 108 patients entered in the study, one patient (#51) was excluded because he received a Brescia-Cimino fistula instead of ePTFE graft after enrollment in the study. Thus, there were 84 Type I patients and 23 Type II patients enrolled into the study. Eleven patients did not complete the protocol. Two of them were lost to follow-up and the remaining were dropped from the study because of transplantation or patient refusal to continue. Ninety-six patients were considered to have completed the protocol (Table 2). For a patient to have completed the protocol, the patient either completed all visits over

Table 1. Patient characteristics

	Treatment groups				
	Dipyridamole	Aspirin	Dipyridamole + aspirin	Placebo	Total
Type I patients					
Age *years*					
Mean ± SD	56.6 ± 15.0	56.7 ± 14.5	51.3 ± 17.8	55.3 ± 10.6	54.9 ± 14.8
Gender					
Male	6	13	7	10	36
Female	17	7	16	9	49
Race					
Black	4	6	6	8	24
White	18	13	17	11	59
Other	1	1	0	0	2
Height *inches*					
Mean ± SD	65.2 ± 3.4	66.9 ± 4.0	65.9 ± 4.0	66.6 ± 4.6	66.1 ± 4.0
Weight *pounds*					
Mean ± SD	155.2 ± 37.5	164.1 ± 29.8	158.1 ± 39.8	161.9 ± 42.8	159.6 ± 37.3
Type II patients					
Age *years*					
Mean ± SD	62.2 ± 16.7	43.0 ± 17.5	48.5 ± 22.2	57.0 ± 15.8	52.5 ± 18.7
Gender					
Male	1	3	2	3	9
Female	5	3	4	2	14
Race					
Black	2	2	2	2	8
White	4	4	4	3	15
Height *inches*					
Mean ± SD	63.5 ± 2.4	63.6 ± 4.7	64.8 ± 3.5	67.4 ± 2.5	64.7 ± 3.6
Weight *pounds*					
Mean ± SD	145.5 ± 31.3	130.4 ± 22.3	166.8 ± 43.0	146.8 ± 17.4	148.2 ± 31.7

Table 2. Outcome

	Treatment groups				
	Dipyridamole	Aspirin	Dipyridamole + aspirin	Placebo	Total[a]
Type I patients					
A. Treated	23	20	22	19	84
B. Complete per protocol					
1. No thrombosis	14	9	13	12	48
2. Thrombosis	4 (17%)	10 (50%)	5 (23%)	6 (32%)	25 (30%)
C. Incomplete per protocol					
1. Lost to follow-up	1	1	0	0	2
2. Other[b]	4	0	4	1	9
Type II patients					
A. Treated	6	6	6	5	23
B. Complete per protocol					
1. No thrombosis	1	3	0	1	5
2. Thrombosis	5 (83%)	3 (50%)	6 (100%)	4 (80%)	18 (78%)

[a] One patient was excluded because he received Cimino fistula instead of ePTFE graft after enrollment into the study. The study population was therefore reduced to 107 patients.
[b] Reasons included patient refusal, transplantation, etc.

18 months, developed a thrombosis (study endpoint), or discontinued from the study due to an adverse event. Thirty-four patients were discontinued from the study due to adverse events.

Outcome in Type I and Type II patients are shown in Table 2. Analyzing crude thrombosis rates for 84 Type I patients suggested a positive effect of dipyridamole and a negative effect of aspirin. Those treated with dipyridamole had half the rate of thrombosis of those not treated with dipyridamole (20% vs. 41%, $P = 0.062$), whereas patients treated with aspirin had higher rates than those treated without aspirin (36% vs. 24%, $P = 0.34$). The lowest rate of thrombosis (17%) occurred in patients treated with dipyridamole alone while the highest rate (50%) occurred in patients treated with aspirin alone. Thrombosis in patients receiving dipyridamole and aspirin combination was 23% while that in the placebo group was 32%.

Using actuarial analysis with Cox proportional hazards model in Type I patients, the beneficial effect of dipyridamole was again evident. Thus, at the end of the 18 month follow-up, the cumulative rates of thrombosis were: 21 ± 9% on dipyridamole

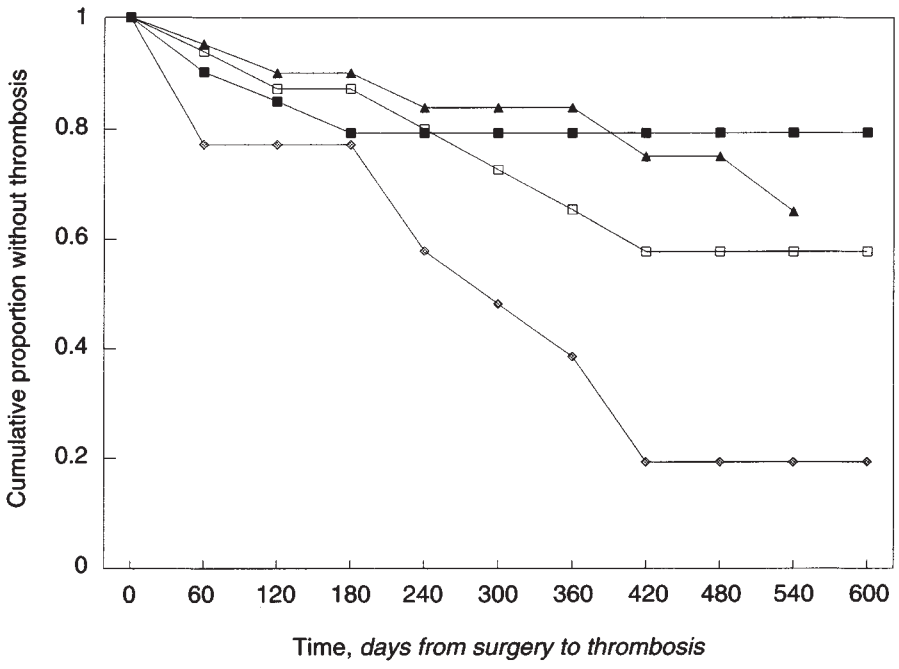

Fig. 1. *Cumulative proportion of ePTFE grafts without thrombosis in Type I patients.* The relative risk of thrombosis with dipyridamole was 0.35 ($P = 0.02$) and relative risk of thrombosis with aspirin was 1.99 ($P = 0.18$). The P values have been multiplied by 2 in order to adjust for subgroup analysis. Symbols are: (■) dipyridamole; (◈) aspirin; (▲) dipyridamole + aspirin; (□) placebo.

Table 3. Adverse events

	Treatment groups				
	Dipyridamole	Aspirin	Dipyridamole + aspirin	Placebo	Total
Total treated	29	26	28	24	107
1. Cardiac[a]	2	2	3	2	9
2. Gastrointestinal[b]	5	3	5	2	15
3. Other					
Headache	3	0	4	1	8
Nausea	2	2	3	4	11
Vomiting	2	1	3	3	9
Miscellaneous	3	2	2	1	8

[a] Six of the 9 patients who experienced cardiac adverse events had prior history of cardiac ischemia before participation in the study.
[b] Five of the 15 patients who experienced GI adverse events had remote history of GI hemorrhage or peptic ulceration before participation in the study.

alone, 25 ± 11% on dipyridamole and aspirin combination, 42 ± 13% on placebo, and 80 ± 12% on aspirin alone (Fig. 1). The relative risk of thrombosis with dipyridamole was estimated to be 0.35 ($P = 0.02$, after adjustment for subgroup analysis) with 95% confidence limits of 0.15 and 0.80. By contrast, the relative risk with aspirin was 1.99 with 95% confidence limits of 0.88 and 4.48. However, this effect was not statistically significant ($P = 0.18$). No evidence of interaction between dipyridamole and aspirin was found ($P = 0.33$).

Type II patients had high thrombosis rates regardless of the treatment group. Overall there was 78% thrombosis in Type II patients and there were no statistical differences between study groups (Table 2). The number of patients per treatment group was too few for actuarial analysis.

Adverse effects

Adverse experiences determined to be either probably or possibly related to the investigational drug(s) were reported by 20 (69%) patients treated with dipyridamole alone, 15 (58%) patients treated with aspirin alone, 18 (62%) patients treated with both dipyridamole and aspirin, and 16 (67%) patients who received placebo. These were not statistically significantly different from each other. The most common serious adverse events were angina pectoris and gastrointestinal (GI) bleeding. Table 3 lists some of the adverse events reported during the study period. Seven deaths occurred during the study, one each in dipyridamole alone and aspirin alone groups, two in dipyridamole and aspirin combination group, and three in the placebo group.

Discussion

Several studies have estimated the probability of thrombosis of PTFE grafts at one year to range from 49 to 72% [6, 7, 15]. In the Canadian Hemodialysis Morbidity Study [16], a multicenter prospective cohort study, the likelihood of graft thrombosis at one year was 39.9%. This is similar to the overall crude thrombosis rate observed in our study (40%). Conservative estimates of the cost of treating access-related complications

have varied from 150 to 500 million dollars per year in the US [1, 2]. These estimates do not include the costs of out-patient treatments provided. Because of the higher rates of thrombosis and infection, the majority of these costs are related to PTFE grafts. In addition, the Canadian hemodialysis morbidity study documented a 2.49-fold increase in the probability of hospitalization for any cause in patients with synthetic vascular access grafts compared to those with autologous vein fistula [16].

The most common mode of synthetic vascular access failure is via stenosis of the graft-venous anastomosis that results from neointimal hyperplasia of the smooth muscle cells and extracellular matrix [17, 18]. Such a stenosis has been shown to be present in at least 67% of all access failures [8]. A recent review [19] discusses the current understanding of the pathogenesis of neointimal hyperplasia. The mechanism that has received most of the experimental support in animal models of graft patency is platelet activation, which can result from the interaction of platelets with foreign (graft) surfaces, as well as from turbulent flow [20, 21]. Once activated, platelets release platelet-derived growth factor (PDGF), thromboxane A_2 and other substances that may promote further platelet aggregation as well as have direct vascular effects. In addition, shear-induced intimal injury and repair also participate in the proliferative response by the smooth muscle cell. Finally, dialyzer membranes also vary in thrombogenicity [22], and may participate in platelet activation [23].

The results of this prospective, double-blind, placebo-controlled study suggest a potentially important role for dipyridamole in preventing graft thrombosis in patients with a new arteriovenous ePTFE graft. Thus, patients on dipyridamole alone had a graft patency rate of 79% at the end of the study, the best patency rate of all study groups, whereas the group on dipyridamole and aspirin combination had the second best patency rate (75%). However, this beneficial effect appears to be specific for Type I (new ePTFE graft) patients only. In patients enrolled in the study after graft thrombosis and a thrombectomy and/or revision (Type II patients) there was no benefit from the use of dipyridamole.

Dipyridamole has been shown to have multiple, possibly synergistic, mechanisms [24] that may explain these results. Dipyridamole inhibits cAMP-phosphodiesterase [25] causing a rise in intracellular cAMP and free calcium in platelets, thus inhibiting platelet activation. Dipyridamole also potentiates the inhibitory effects of adenosine on platelet function by blocking reuptake by vascular and blood cells [24]. It potentiates the anti-aggregatory effects of prostacyclin [26] and enhances prostacyclin biosynthesis [27]. Dipyridamole has been shown to increase 13-hydroxyoctadecadienoic acid (13-HODE) production by endothelium making the vessel wall less "adhesive" to platelets [28]. These mechanisms lead to inhibition of platelet adhesion to subendothelium and prosthetic materials [29], platelet release reaction and platelet aggregation [30]. Finally, dipyridamole has been shown to decrease serum PDGF level, and selectively decrease the level of fibroblast mitogenic activity (a biological marker of PDGF) whereas aspirin does not possess such effects [31].

In addition to these *in vitro* defined mechanisms, the results of several large clinical trials support the advantages of adding dipyridamole to aspirin. In the "Group Español para el Seguimiento del Injerto Coronario" (GESIC) study [32], only the outcome in the aspirin/dipyridamole combination group was significantly better than placebo, whereas the group treated with aspirin alone was not. In a meta-analysis of 25 trials of anti-platelet treatment including 29,000 patients [33], the Anti-platelet Trialists' Collaboration found that the combination of aspirin and dipyridamole decreased new vascular events 31% compared to only 24% with aspirin alone. More recently Weber et al [28] demonstrated that in rabbits treated with dipyridamole, vessel wall thrombogenicity was decreased by half whereas those treated with salicylate had a twofold increase, a highly significant difference. They attributed the beneficial effect of dipyridamole to the increase in 13-HODE synthesis.

The explanation for the lack of benefit from dipyridamole in Type II patients is conjectural. The presence or extent of proximal venous stenoses was not systematically examined in this study. Schwab and others [34–36] have shown in several studies that the presence of these stenoses is strongly associated with subsequent thrombosis of the graft, while their correction by surgery or angioplasty significantly improves the prognosis for graft patency. Thus, the presence of such proximal venous stenoses may have contributed to the lack of pharmacological benefit from any treatment in Type II patients. Indeed, graft survival rates were extremely poor in all groups of Type II patients in this study and the overall rate of re-thrombosis was 78% (18/23 patients).

An unexpected result of this study was the fact that aspirin therapy was associated with an increase in the development of fistula thrombosis in patients receiving new ePTFE grafts compared to dipyridamole and placebo. Although we did not study the mechanism(s) of such an increase it is possible that cyclooxygenase inhibition by aspirin may shift platelet arachidonic acid metabolism in the direction of 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) production via platelet-derived 12-lipoxygenase. 12-HETE has been shown to mediate the PDGF-induced chemoattraction of vascular smooth muscle cells [37, 38]. Thus, platelet cyclooxygenase inhibition may paradoxically enhance the development of neointimal hyperplasia and increase rate of graft thrombosis. Recent studies also suggest that aspirin does not inhibit the interaction of platelets with monocytes and polymorphonuclear cells, its expression of P-selectin, nor its ability to release α-granules which contain PDGF [39]. It is also possible that the dose of aspirin used in this study blocked the production of prostacyclin by the endothelial cells, thus abrogating the anti-aggregatory effects of prostacyclin [40]. Finally, Weber et al have demonstrated that salicylate was associated with decreased 13-HODE synthesis and increased platelet adhesion whereas dipyridamole had opposite effects [28]. Further research will be needed to confirm these observations and to define the relative mechanisms in uremic patients. Nevertheless, these results along with others [41–43] suggest that aspirin can have effects in uremic patients different from normal controls.

Despite the apparent promise of dipyridamole in preventing graft thrombosis in newly placed ePTFE grafts reported in this study, it is important to point out the limitations of such a conclusion. First, the efficacy of dipyridamole was seen at a time when EPO was not routinely used. Additionally, this study was conducted in a single center. Thus, further studies to confirm the potentially beneficial effects of dipyridamole and adverse effects of aspirin will need to be undertaken. Finally,

although there were no statistically significant differences in the incidence of side effects among different treatment regimens including the group on placebo, all were relatively high. It is possible that lower doses of the drugs, particularly dipyridamole, may be equally effective, but with fewer side effects.

More importantly, this study points out the magnitude of the problem of access failure and the urgent need for more innovative methods to reduce this high incidence. Newer strategies like heparin bonding to graft material [44], use of low molecular weight heparin [45] and materials with decreased thrombogenicity [44, 46], as well as endothelial seeding of the graft material [47] may also be helpful but, obviously, need further investigation. Finally, other pharmacologic interventions to prevent HD vascular access thrombosis as has been recently reviewed should be considered [48].

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