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Clopidogrel diminishes hemodialysis access graft thrombosis

H. TRIMARCHI[1], P. YOUNG[2], M. FORRESTER[1], J. SCHROPP[1], H. PEREYRA[1], E. FREIXAS[1]

[1]Nephrology Section, and [2]Internal Medicine Section, Department of Medicine, Hospital Británico de Buenos Aires - Argentina

Abstract: ***Background:*** **The most common complication of hemodialysis access graft is thrombosis. Clopidogrel, an inhibitor of platelet aggregation, was assessed to prevent this serious complication.**
Methods: **Nineteen patients on chronic hemodialysis whose vascular accesses were grafts were divided into two groups: Group A (n=11, 58%) consisted of patients who did not receive anti-thrombotic therapy after graft placement; Group B (n=8, 42%) received clopidogrel 75 mg/day from two days after surgery onwards. Both groups were well matched with respect to age, gender, cause of renal failure, hematocrit, platelet count and Kt/V. All patients' thrombotic episodes were followed up from the day of graft surgery until thrombosis was diagnosed. Finally, the survival difference between both groups was determined.**
Results: **Ten thrombotic episodes were diagnosed in Group A while no events were reported in Group B ($p<0.001$). Graft access days of patency were significantly more in Group B than in Group A (350.8±166 *vs* 86.8±69, $p<0.001$). The time elapsed from dialysis initiation to graft placement was not different (Group A: 18±12 days; Group B: 20±10 days). Days in hemodialysis were different between both groups (Group A: 195.9±96; Group B: 545.5±291, $p<0.001$) and all patients of Group A (n=11, 57.9%) and two patients of Group B (25%) died ($p=0.001$). No major bleeding events were reported.**
Conclusions: **Clopidogrel significantly decreased thrombotic graft episodes. Patients on clopidogrel had a prolonged vascular access patency, longer time on hemodialysis and longer survival. (The Journal of Vascular Access 2005; 6: 29-33)**

Key words: *Clopidogrel, Hemodialysis, Graft, Vascular access, Thrombosis, Fistula, Atherosclerosis*

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INTRODUCTION

Hemodialysis requires access to blood vessels capable of providing rapid blood flow, mainly achieved by native fistulas and synthetic polytetrafluoroethylene grafts. However, complications associated with vascular access often occur. Vascular access complications are not only a major cause of morbidity in hemodialysis patients but also a major cost, accounting for approximately 20% of the total spending for hemodialysis patients in the United States (1). In addition, many reports confirm that access-related morbidity comprises almost 25% of all hospital admissions for end-stage renal disease patients and may contribute to as much as 50% of all hospitalization costs (1-4).

Thrombosis is considered the most frequent complication of vascular grafts and, when not corrected, accounts for more than 80% of arteriovenous access loss. The major predisposing factor is anatomic venous stenosis, which is responsible for 85% of thromboses (1, 5).

In addition to correcting stenotic lesions, several pharmacological strategies have been attempted to lower the risk of thrombosis associated with chronic vascular access. These attempts included treatment with dipyridamole, low-dose aspirin with or without sulfinpyrazone, and aspirin plus clopidogrel (6-8). However, due to conflicting results, the role of antiplatelet agents in preventing access thrombosis remains unclear.

We decided to assess the risk of thrombosis in syn-

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thetic polytetrafluoroethylene grafts in patients receiving 75 mg of clopidogrel daily.

MATERIALS AND METHODS

Study design

Nineteen chronic hemodialysis patients with synthetic polytetrafluoroethylene grafts were divided into two groups according to the prescription of clopidogrel. Group A consisted of eleven patients (58%) who did not receive anti-platelet medication after surgery, while Group B consisted of eight patients (42%) who were started on clopidogrel two days after graft placement. Graft patency was monitored until thrombosis was diagnosed and patient survival from graft surgery until the writing of this manuscript was determined.

Patient characteristics

Nineteen chronic hemodialysis patients with synthetic grafts were included. Exclusion criteria were malignancy, end-stage chronic heart disease, active liver or thyroid disease, uncontrolled diabetes mellitus, moderate or severe malnourishment, hematocrit <32% or >36%, or acute infections. The patients were divided into two groups according to the use of clopidogrel. Group A consisted of eleven patients (58%) who did not receive clopidogrel, while group B comprised eight patients (42%) who were prescribed 75 mg of clopidogrel/day; both groups were well matched with respect to age, gender, time on hemodialysis from the initiation of replacement therapy to graft placement, cause of renal failure, baseline hematocrit, baseline homocysteine, and Kt/V (Tab. I). High-flux hemodialysis was performed with a bicarbonate bath, mean Qd 500 ml/minute and mean Qb 350±50 ml/minute. Biocompatible membranes were used: polysulphone F80® (Fresenius Germany) and cellulose triacetate FB210® (Nipro, Japan). Each dialysis session averaged 3.5±0.5 hours thrice weekly.

Vascular access

Group A: Eight patients had radiocephalic grafts (forearm) and three had brachiocephalic grafts (upper arm). *Group B:* Five patients had radiocephalic and three had brachiocephalic grafts. In accordance with the routine protocol of our center, if venous outflow occlusion was diagnosed the patient would be immediately referred to the vascular surgery service for prompt resolution of the stenosis.

Thrombophilic factors

Only in cases where thrombotic events were reported did we investigate other causes of thrombophilia. This consisted of screening for factor V Leiden mutations, prothrombin G20210A variants, and protein C, protein S or antithrombin III deficiency.

Common medications prescribed

All patients received alpha-erythropoietin (2000-4000 U subcutaneously three times a week) post-dialysis and intravenous iron saccharate to reach a transferrin saturation between 20% and 50%. Three thousand units of standard heparin were routinely given to all patients as an infusion by means of an automatic pump during the whole length of each dialysis session. All patients received folic acid (10 mg/day orally) and IV complex B vitamins (postdialysis).

Statistical analyses

Results are expressed as mean ± standard deviation of the mean (SD), unless specified otherwise. The Mann-Whitney *U* test was used for differences in quantitative variables between groups. The chi-square or Fisher test was used for qualitative variable comparisons.

TABLE I - PATIENT CHARACTERISTICS

Group (%)	Male (%)	Age (years)	Hct (%)	Hcy (µmol/L)	Kt/V	DM (%)	SLE	ISCH NEP (%)	GN (%)
A=11 (58)	4 (36.4)	64.0±13.8	33.2±0.8	11.2±2.4	1.1±0.2	2 (18.2)	2 (18.2)	3 (27.3)	4 (36.4)
B= 8 (42)	5 (62.5)	77.0±15.1	32.9±0.7	11.9±2.5	1.2±0.3	2 (25)	1 (12.5)	1 (12.5)	4 (50)

HD, hemodialysis; Hct, hematocrit; Hcy, homocysteine; DM, diabetes mellitus; GN, glomerulonephritis; SLE, systemic lupus erythematosus; ISCH NEP, ischemic nephropathy. Differences are not statistically different

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RESULTS

Patient characteristics

The two patient groups were well matched with respect to age, gender, cause of renal failure, time on hemodialysis to graft placement, time to initiation of graft use, baseline hematocrit, platelet count, homocysteine level and Kt/V (Tab. I). Hemodynamic instability during dialysis sessions was similar among patients of both groups. No cases of factor V Leiden mutations, prothrombin G20210A variants, or protein C, protein S or antithrombin III deficiency were found in these patients.

Vascular accesses

Group A
All grafts thrombosed in this group. Arteriographies confirmed the presence of venous outflow obstruction. No episode of graft thrombosis could be resolved surgically and catheters were transiently inserted. All patients were monitored subsequent to the event to record the complete duration of their dialysis treatment. All patients in Group A died. The time elapsed from graft thrombosis to death was 68.1±15 days. In none of the patients was graft thrombosis attributable to acute predisposing factors (infection, cancer, chronic hypotension).

Group B
No thromboses were recorded in this group. Two patients (25%) died with their grafts functioning. The cause of death was advanced cardiac insufficiency in both cases.

Intergroup results

Ten thrombotic events were diagnosed in Group A while no thromboses occurred in Group B (10 *vs* 1, p<0.001) (Tab. II). The time elapsed from first dialysis to graft placement was similar in both groups: Group A, 18 ± 12 days *vs* Group B, 20±10 days. Also the time from surgery to graft use was similar: Group A, 38 ± 12 days vs. Group B, 37±15 days. Graft patency was significantly longer in Group B compared to Group A: 350.8±166 vs. 86.8±69 days, p<0.001. Days in hemodialysis from first session to death in Group A or to the end of this study in Group B were statistically different: Group A: 195.9±96 *vs* Group B: 545.5±291, p<0.001. Patient survival was statistically longer in Group B (89.5% *vs* 0%, p = 0.001).

Side effects of clopidogrel

At the prescribed dose of 75 mg daily, no major side effects occurred. Although no bleeding time tests or standard coagulation profiles were asked, none of the patients reported clinically evident major bleeding episodes in the gastrointestinal tract, female genital tract, airways or skull. Moreover, skin hematomas and post-dialysis graft bleeding were not different between patients of either group.

DISCUSSION

The present study shows that clopidogrel at a dose of 75 mg daily significantly reduced thrombotic events in polytetrafluoroethylene hemodialysis grafts, thereby increasing the useful life of this type of vascular access. Moreover, duration of hemodialysis treatment and patient survival were longer in this population. Finally, clopidogrel was well tolerated by all patients and no major side effects were reported.
Several aspects need to be mentioned about the present study. The thrombotic episodes in Group A could not be due to early vascular access, to acute or clinical conditions that could predispose to graft occlusion, or to patient characteristics, because in

TABLE II - FINAL RESULTS

Group	Time from HD to graft placement (days)	Time from graft placement to graft use (days)	Graft patency (days)	Time on HD (days)	Total thromboses	Number of deaths	Patient survival (%)
Group A	18.0±12	38.0±12	86.8±69	195.9±96	10	11 (100%)	0
Group B	20.0±10	37.0±15	350.8±166	545.5±291	0	2 (10.5%)	89.5
p	Ns	Ns	<0.001	<0.001	<0.001	= 0.001	= 0.001

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Group B these conditions were highly similar. Although several reports assure that grafts can be used almost immediately after surgery, we start using them only after the soft tissue edema has disappeared and the prosthesis can be clearly felt by the physician and dialysis technician. Doppler sonograms are usually performed before applying the grafts to confirm the clinical impression.

As to the longer survival of Group B (Tab. II), this could be due to a lower rate of thrombotic complications, which, if not surgically corrected, would be followed by hospitalizations, catheter insertions, catheter-associated complications and lower hemodialysis efficacy rates.

Cardiovascular disease is the main cause of death in the end-stage renal disease population (9, 10). Goldsmith et al reported an angiographically confirmed prevalence of significant coronary stenosis that varied from 24% in a young non-diabetic hemodialysis population to 85% in long-standing diabetic dialysis patients over 45 years of age (11). Moreover, most hemodialysis patients with angiographically significant coronary artery disease are symptomless (12). In this regard, the CAPRIE study has shown that clopidogrel is effective in reducing ischemic events in patients with myocardial infarction in the general population (13). Thus, another reason why clopidogrel may prolong patient survival in uremic patients could be its cardioprotective effect. It should be noted that the two patients of Group B who died had their grafts functioning by the time of death.

Uremic patients have an acquired functional platelet defect favoring bleeding. However, increased platelet adhesiveness in atherosclerotic uremic patients has also been reported (11). Although coagulation studies were not performed in the present study, patients on clopidogrel did not show evidence of major bleeding events, and hematocrit falls or clinical overt hemorrhagic episodes were not reported. Moreover, minor post-dialysis bleeding at the puncture site of the graft was similar in both groups. Data on the use of clopidogrel alone in this population are lacking, but a recent study suggests that the dose of clopidogrel need not be adjusted in patients with moderate to severe renal failure, although it prolongs the bleeding time almost two-fold (14, 15). Moreover, a pharmacodynamic study of clopidogrel in chronic hemodialysis patients indicated that the inhibition of platelet aggregation is safe and unaltered by hemodialysis (16).

Clopidogrel is a thienopyridine derivative that achieves its antiplatelet effect by inhibiting the binding of adenosine diphosphate (ADP) to its membrane receptor. Its antiplatelet aggregation is concentration dependent and appears to be highest after four to seven days of therapy at the standard dose of 75 mg daily, at which time 30% to 50% of platelet aggregation is inhibited. This antiplatelet effect is irreversible. Clopidogrel is extensively metabolized by the liver, and approximately 50% of the drug is excreted in the urine (16).

The most common complication of chronic hemodialysis vascular access is thrombosis, which, when not corrected, accounts for approximately 85% of vascular loss (1, 5, 17). Grafts are 3.8 times more likely to require a thrombectomy and 3.0 times more likely to need access intervention than native fistula (18). One of the main reasons for this increased predisposition to develop thrombosis is their propensity for venous outflow stenosis caused by endothelial and fibromuscular hyperplasia. In addition, failure of permanent vascular access in hemodialysis patients occurs in 80% of cases due to thrombosis (1, 5, 17). Finally, only 50% of arteriovenous grafts survive longer than three years (19). In this respect, clopidogrel does not solve venous outflow stenosis, but it may diminish platelet adhesion to turbulent partially occluded flows, probably slowing the rate of thrombosis and vessel occlusion.

Strategies to prevent thrombosis other than treatment of venous outflow stenosis in hemodialysis patients are scant and include dipyridamole and low-dose aspirin and aspirin plus clopidogrel (6-8). The first combination did not appear to be effective in patients with previous thrombosis, although the thrombosis rate in patients with new grafts was substantially reduced with dipyridamole (6). A recent study assessed the effectiveness of aspirin plus clopidogrel in preventing graft thrombosis. This approach would affect platelet activation in two ways: cyclo-oxygenase activation and thromboxane generation by aspirin plus platelet ADP binding by clopidogrel. However, the study was interrupted because of a markedly increased risk of bleeding among those under treatment (8). Our results show that clopidogrel alone can be used safely to prolong graft survival in chronic hemodialysis patients and may also contribute to cardioprotection.

In our study, clopidogrel significantly decreased thrombotic graft episodes. Patients on clopidogrel had prolonged vascular access patency, a longer time on hemodialysis and better survival. We are aware that the study involved a very small number of patients, but in view of the promising results we believe that our preliminary findings

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deserved prompt communication. However, the data must be interpreted with caution because the pharmacological approach to prevent vascular access thrombosis in hemodialysis is still in its infancy. A prospective randomized controlled trial including a larger number of patients is warranted.

Address for correspondence:
Dr. Hernán Trimarchi
Hospital Británico
Perdriel 74
1280 Buenos Aires - Argentina
htrimarchi@hotmail.com

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