Clopidogrel versus acetyl salicylic acid in arteriovenous fistula salvage

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Background
The optimal vascular access for chronic hemodialysis is the arteriovenous fistula (AVF). Several studies suggest a role for antiplatelet agents in the prevention of early AVF failure.

Aim of the study
This trial was conducted to assess the efficacy and safety of clopidogrel versus acetyl salicylic acid in hemodialysis patients.

Patients and Methods
A total of 50 patients received 75 mg/day of clopidogrel, 50 patients received 150 mg/day of acetyl salicylic acid, and 50 patients served as the control group. The treatment was initiated 7–10 days before the surgery and continued up to 6 weeks postoperatively; thereafter, patients were monitored for 6 months.

Results
The primary outcome was AVF failure 8 weeks after fistula creation. The primary AVF failures at 2 months were 32.5% in the acetyl salicylic acid group and 6.6% in the clopidogrel group. First hemodialysis from newly created AVF in the clopidogrel group was significantly more successful than that in the acetyl salicylic acid group. No life-threatening adverse event or severe bleeding was recorded in both groups.

Conclusion
Clopidogrel seems to be effective and safe compared with acetyl salicylic acid in the prevention of primary AVF failure in hemodialysis patients.

Keywords:
acetyl salicylic acid, arteriovenous fistula, clopidogrel, hemodialysis, primary arteriovenous fistula failure

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Introduction

For efficient hemodialysis, creation of a working arteriovenous fistula (AVF) is a must. Because of the long life span and fewer complications, the AVF is considered as the best venous access for chronic hemodialysis patients [1]. There are certain criteria that must be reached before the usage of the fistula, such as vein diameter and peak systolic velocity [2]. Fistula failure is the most dramatic morbidity that can occur after fistula creation due to thrombosis, failure of the vein to reach certain diameter, or low-flow across the fistula [3]. Early fistula failure (between 4 and 6 weeks) is not uncommon and it occurs in about 7–40% of all cases. Difficulty in venous access and failure to maintain enough flow to keep the dialysis machine working are the most frequent manifestations of shunt failure [4–6]. Therefore, early fistula assessment of patency and flow is recommended [7]. Many authors reported that the use of antiplatelet agents can prevent early fistula failure [8–18]. On the basis of this, we performed our study to compare the most common antiplatelet agents in primary fistula salvage.

Patients and methods

The study was conducted at Zagazig University Hospitals Vascular Outpatient Clinic from April 2013 to April 2014. Patients older than 18 years of age with chronic renal failure requiring hemodialysis with suitable vascular condition for constructing radiocephalic shunt were included in the study. Exclusion criteria were as follows: patients with a history of previous bleeding episodes within 6 months before initiation of the study, patients already receiving chronic anticoagulation therapy (antiplatelet agents or warfarin), patients with terminal or life-threatening disease, pregnancy, malignant hypertension, a platelet count less than 100 000/mm^3, and other demonstrated medical conditions that would make antiplatelet therapy dangerous.

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A total 150 consenting eligible participants were divided into three groups: the acetyl salicylic acid group included 50 patients who received 150 mg of acetyl salicylic acid; the clopidogrel group included 50 patients who received 75 mg of clopidogrel; and the control group included 50 patients who did not receive any antiplatelet. The treatment was initiated 7–10 days prior surgery and continued up to 6 weeks postoperatively with full approval by the ethical committee in our university. Patients were monitored for occurrence of complications and need for hemodialysis until 6 months after trial.

The primary endpoint was AVF failure 8 weeks after fistula creation. The fistula was classified as patent if a bruit was detectable along the vein proximal to the arteriovenous anastomosis throughout systole and diastole. Secondary endpoint was 6 months later. Platelet hemostatic functions [platelet aggregometry, flow cytometry, and bleeding time (BT)], mainly BT, were evaluated monthly. Detailed information on bleeding events was obtained. The study drug was discontinued following any bleeding event.

Statistical analysis

Data collected on history, basic clinical examination, laboratory investigations, and outcome measures were coded, entered, and analyzed using Microsoft Excel software (USA). Data were then imported into the statistical package for the social sciences (SPSS, version 20.0; SPSS Inc., Chicago, Illinois, USA) software for analysis. On the basis of the type of data, the following tests were used to test differences for significance. Differences between frequencies (qualitative variables) and percentages in groups were compared using the χ^2-test. Differences between means (quantitative variables) in two parametric groups were determined using *t*-test. Odds ratio (OR) was used for risk assessment; *P* value was set at less than 0.05 for significant results and at less than 0.001 for highly significant results.

Results

Between April 2013 and April 2014, a total of 150 patients met our inclusion criteria and were enrolled in our study. The laboratory findings for each group are summarized in Table 1. There were no significant differences in covariables between the groups. None of the covariables (covariables thought to influence the risk for AVF included age, sex, diabetes mellitus, BT, and blood pressure) measured at baseline or follow-up correlated with the development of AVF failure. All patients had been taking the study medication since 7–10 days before surgery. However, the medication had to be discontinued prematurely in 15 (10.0%) patients because of withdrawal from the trial in the case of five patients and complications in the case of 10 patients. Finally, 135 patients completed the trial: 45 patients in the clopidogrel group, 40 patients in the acetyl salicylic acid group, and 50 in the control group.

Table 1 Covariables thought to influence the risk for arteriovenous fistula

Risk factor	Clopidogrel (*N* = 45)	Acetyl salicylic acid (*N* = 40)	Control group (*N* = 50)	*P*
Age (mean ± SD)	45.6 ± 9.5	44.9 ± 12.6	44.1 ± 10.9	0.87
Sex [*n* (%)]				
Male	25 (55.5)	22 (55.0)	28 (56.0)	0.99
Female	20 (44.5)	18 (45.0)	22 (44.0)	
DM [*n* (%)]	12 (26.6)	11 (27.5)	13 (26.0)	0.97
SBP (mean ± SD)	136.6 ± 29.5	134.9 ± 31.9	138.5 ± 32.2	0.82
DBP (mean ± SD)	85.6 ± 18.7	84.9 ± 20.7	88.3 ± 22.5	0.64

DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure.

During follow-up from 8 weeks to 6 months no important complication occurred. Hemodialysis was performed for 45 patients of the clopidogrel group within 6 months after AVF creation and it was successful in 42 patients (failure was 6.6%). In the acetyl salicylic acid group, hemodialysis from the AVF was performed for 40 patients and it was successful in 27 cases (failure was 32.5%); both groups were significantly successful compared with the control group in which dialysis was successful in 22 cases (failure was 56%). First dialysis from the AVF in the clopidogrel group was significantly more successful than that in the acetyl salicylic acid group (*P* = 0.0004; Table 2). The higher percentage of failure cases in groups B (aspirin) and C (control) may be attributed to loss to follow-up (mostly good responders with successful fistula were not interested in follow-up) and nonrandomization; therefore, good responders were selected to be exposed to drugs, whereas patients with poor general conditions were taken as controls. No severe bleeding episodes such as intracranial hemorrhage were recorded during the active treatment period. There were no deaths due to bleeding in either treatment group. BT s were similar at baseline for the clopidogrel group (8.1 ± 0.3 min) and the acetyl salicylic acid group (8.4 ± 0.6 min) and remained stable (8.5 ± 0.4 min) for the clopidogrel group and 8.6 ± 0.3 min for the acetyl salicylic acid group throughout the study period. After 6 months the BT was 8.3 ± 0.8 min in the clopidogrel group and 8.5 ± 0.7 min in the acetyl salicylic acid group (Table 3).

Discussion

Successful hemodialysis requires function venous accesses. The AVF is the method of choice for hemodialysis in patients with chronic renal failure [1].

Table 2 Arteriovenous fistula failure

Item failure	Clopidogrel	Acetyl salicylic acid	*P*	OR (95% CI)
AVF failure	3 (6.6)	13 (32.5)	0.0004**	6.74 (1.57–33.3)*
	Clopidogrel	Control	*P*	OR (95% CI)
AVF failure	3 (6.6)	28 (56.0)	0.001**	17.8 (4.44–83.2)*
	Acetyl salicylic acid	Control	*P*	OR (95% CI)
AVF failure	13 (32.5)	28 (56.0)	0.012*	2.64 (1.02–6.92)*

Values are represented as *n* (%); AVF, arteriovenous fistula; CI, confidence interval; OR, odds ratio; **Significant.

Table 3 Bleeding time

Time of bleeding	Clopidogrel (mean ± SD)	Acetyl salicylic acid (mean ± SD)	Control (mean ± SD)	*P*
Bleeding time at baseline	8.1 ± 0.3	8.4 ± 0.6	8.2 ± 1.2	0.29
Bleeding time post-treatment	8.5 ± 0.4	8.6 ± 0.3	8.1 ± 0.9[a]	0.0004**
Bleeding time after 6 month	8.3 ± 0.8	8.5 ± 0.7	8.2 ± 1.0	0.26

[a]Group caused the significance; **Significant.

The fistula is relatively easy to perform under local anesthesia and has a relatively low rate of complications. However, a significant proportion (8–12%) of fistulas fail early within 3 months of surgery [4–6]. Primary fistula failure is defined as a fistula that never provided successful hemodialysis [18]. Venous access failure is the most common reason for hospitalization among hemodialysis patients [19]. The typical lesion of access thrombosis is neointimal vascular smooth muscle cell proliferation in the anastomotic draining vein. Platelet activation from endothelial injury may play an important role in stimulating platelet aggregators such as platelet drived growth factor (PDGF) and thromboxane A2, in addition to directly stimulating vascular intimal proliferation [18]. Therefore, the preventive effect of antiplatelet agents, including acetyl salicylic acid, dipyridamole, ticlopidine, and clopidogrel, was tested [9–17]. Our study was conducted to compare the efficacy and safety of clopidogrel with that of acetyl salicylic acid in the prevention of primary AVF failure. We observed a significant risk reduction in the primary AVF failure in the clopidogrel treatment group compared with the acetyl salicylic acid group and the control group. The results of our analysis suggest that daily administration of 75 mg of clopidogrel, beginning 7–10 days before AVF creation, was successful in preventing the development of vascular failure with acceptable side effects. This finding suggests that the risk reduction in vascular failure might be attributed to clopidogrel administration. Our results are supported by the recent report by Cochrane [20]. This meta-analysis shows the effect of clopidogrel treatment as an adjuvant to increase the patency of AVFs in the short term. Yevzlin *et al.* [22] showed a negative association between antiplatelet therapy and access patency. Kaufman *et al.* [23] demonstrated no change in the risk of graft thrombosis with acetyl salicylic acid versus clopidogrel therapy. They also noted that, in chronic hemodialysis patients, there is a trend toward increased thrombosis with acetyl salicylic acid therapy. Moreover, Kaufman *et al.* [23] were unable to demonstrate a benefit with low-dose acetyl salicylic acid on thrombovascular events in 68 hemodialysis patients. In contrast, in all studies of clopidogrel in patients with new primary fistulae, the thrombosis rate was significantly less than that in the aspirin group [20]. In a study by Gröntoft *et al.* [13], only two out of 19 who received treatment developed fistulae thromboses compared with eight out of 17 on placebo [OR = 0.13, 95% confidence interval (CI) 0.02–0.76]. In 1998, Gröntoft *et al.* [14] reported that 16 out of 130 patients who received clopidogrel developed thromboses in the fistulae compared with 25 out of 131 in the placebo group (OR = 0.60, 95% CI 0.30–1.18). The overall result of the meta-analysis also favored treatment (OR = 0.47, 95% CI 0.26–0.85). The overall *P* value was 0.01 [20]. These data are in agreement with those of CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) study, which proved the superiority of clopidogrel as an antiplatelet, because the ADP receptor blockers (clopidogrel) are more potent than COX-1 in activators (aspirin) [21].

The overall incidence of bleeding events was 3% in our study. According to Kaufman and colleagues, we expected to encounter 16 episodes of bleeding during the 6 months in our patients [22–23]. However, the incidence of bleeding episodes was lower than expected. This finding might be related to restrictive exclusion criteria.

Conclusion

Clopidogrel has the upper hand over acetyl salicylic acid in the prevention of early fistula failure in chronic renal failure patients. Beginning 7–10 days before AVF creation and continuing for 6 weeks, seems to prevent primary AVF failure with acceptable side effects in selected hemodialysis patients.

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Conflicts of interest
There are no conflicts of interest.

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