The Effect of Ticlopidine on Early Arteriovenous Fistula Thrombosis: A Randomized Clinical Trial

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Abstract

Background: Arteriovenous (AV) fistula is the first choice of a long-term vascular access for hemodialysis, but there is a 20-30% probability of thrombosis in the 1st month after its creation. Ticlopidine is a potent drug, which inhibits both primary and secondary platelet aggregation. This study is performed to evaluate the effect of ticlopidine in the prevention of AV fistula.

Methods: Totally 124 patients in need of an AV fistula were divided into two groups after creation of their fistula. In the first group, we prescribed ticlopidine for 62 patients, and in the second group, 62 patients received placebo. The two groups were compared to see if their fistulas are patent or thrombotic after 1 and 3 months.

Results: Of the 62 patients who received ticlopidine, four had fistula thrombosis, while in 62 patients who received placebo, 16 had fistula thrombosis (P = 0.003). This shows the significant effect of ticlopidine in the prevention of thrombosis in AV fistulas. Also, we compared age, sex, and the fistula location in the ticlopidine and placebo groups, and these attributes had no significant difference between the two groups (P > 0.050).

Conclusions: Considering the significant value of ticlopidine in the prevention of AV fistula thrombosis, it can be recommended after the surgery if there is no contraindication for its use.

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Introduction

The arteriovenous (AV) fistula is the preferred type of vascular access because thrombosis rates, infection rates, access-related expenditures, and total health-care expenditures all are lower for patients with fistulas than for those with either synthetic AV grafts or central venous catheters (1-3). The first AV fistula was used in 1966 (1), and it is still the first priority to have a long-term vascular access for hemodialysis. However, a substantial problem is the fistula thrombosis during the first weeks after surgery (4,5).

Antiplatelet agents such as acetylsalicylic acid and sulphinpyrazone have been used to prevent fistula thrombosis, but they have not shown favorable results (6-10). Ticlopidine is a potent inhibitor of both primary and secondary platelet aggregation (11,12). It reaches its peak effect in 5-6 days (13). In other studies, after 1 month of treatment with ticlopidine, the incidence of fistula in the 1st month has reduced from 30% in the placebo group to 10% in patients who received ticlopidine (14-17).

Prevention of fistula thrombosis not only reduces the surgery's adverse effects and the need to reoperation, but also it considerably reduces patient's hospitalization time and costs. If ticlopidine gets approved in the prevention of early fistula thrombosis, it will be an important achievement in post-surgical care of hemodialysis patients.

Materials and Methods

The study population comprised 124 patients who were referred to a general hospital's surgery ward for surgical application of an AV fistula between 2012 and 2014. 61 patients were male and 63 were female. After proper explanation of the study and obtaining an informed consent, the patients were randomly divided into two groups: The first group of 62 patients received a 250 mg tablet of ticlopidine every 12 hours and the second group received placebo tablets. Generally, the patients were referred from nephrologists or general surgeons for kidney disorders which had caused them to be dependent on dialysis, or would have made them dialysis-dependent in the future.

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The maximum age to enter the study was 85 years, and the patients who suffered from hepatic diseases, malignant hypertension, peptic or duodenum ulcers, or coagulopathies were excluded from the study.

The patients were checked to see if their fistulas are patent or not, once 4 weeks after surgery and then again 3 months after surgery. The fistula location was checked to see if there is a thrill, and the uncertain cases were evaluated by a radiologist using Doppler sonography. All surgeries were performed by a vascular surgeon in the hospital's operation room. The patients whose fistula failed once could return to the study after a period of 3 weeks. The type of study was interventional (randomized controlled trial). The drug (ticlopidine) and the placebo tablets were both produced in Iran by Osvah Pharmaceutical Company. The placebo tablets had the exact same look as the drug, and the costs were covered by the study's sponsors.

Sampling method: The patients were randomly designated to one of the groups using block randomization method. The order of patients was obtained from hospital's research and development center in closed envelopes which were opened after the patient's surgery. We used a unique file to store every patient's data. The patient blinding process was as follows: None of the patients were aware if they are receiving a drug or placebo. The drug tablets and the placebo tablets had similar shape, packaging, taste, and color.

Follow-up: The patients were followed up twice, once after 4 weeks and again after 3 months, in the vascular surgery clinic. The thrombosis was diagnosed by the vascular surgeon who performed the surgery, and if a patient did not have any thrill, he/she was referred to a radiologist to perform a Doppler sonography. The patients' information involving their telephone numbers was registered, and if a patient did not come to the clinic for follow-up visits, the researcher contacted them and encouraged them to apply for a follow-up visit.

Ethical considerations: The research was completely described to the patients, and written informed consents were obtained. The patients' information remains confidential. The drug and placebo costs were provided by the study's sponsors. Doppler sonography was performed only when there were scientific indications, and the patients did not need to pay for the test. The patients were able to leave the study whenever they wanted to.

Results

Of the 124 patients, 61 (49.2%) were male and 63 (50.8%) were female. Minimum age was 19 years and maximum age was 79. The calculated chi-square test value was 0.857 for sex and 0.241 for age, which shows normal distribution of these attributes (Table 1).

In the patients who received ticlopidine, 4 of the 62 cases did not have a thrill after 1 month, which were confirmed to have a fistula thrombosis using Doppler sonography. In those who received placebo, 16 of the 62 cases (25.8%) did not have a thrill after 1 month, and they also were all confirmed to have thrombosis by Doppler sonography. The $P = 0.003$, which shows a statistically significant difference between the two groups (Table 2).

We compared age, sex, and the fistula location in the ticlopidine and placebo groups, and these attributes had no significant difference between the two groups ($P > 0.050$).

We also compared the accompanying diseases (diabetes mellitus, hypertension, end-stage renal disease, and collagen vascular diseases) between the ticlopidine and placebo groups, and there were no significant difference between the groups ($P > 0.050$). Of all the patients, only 7 had collagen vascular diseases, so the P value was not reliable in this group of accompanying diseases.

Discussion

In this study, of the 62 patients who received ticlopidine, 4 had fistula thrombosis, while in the placebo group, 16 of the 62 patients had fistula thrombosis ($P = 0.003$), and the significant difference between the two groups justifies the prescription of ticlopidine to prevent AV fistula thrombosis. The sample size of the current study seems to be enough for that conclusion, considering the sample size of the previous studies.

Table 1. Distribution of basic characteristics in the two studied groups

Variables	Levels	Studied groups		Total
		Case group	Control group	
Mean age	Year	53.16	50.48	51.82
Age groups	< 40	10	12	22
	40-50	14	21	35
	50-60	17	14	31
	> 60	21	15	36
Sex	Male	31	30	61
	Female	31	32	63

Table 2. Comparison of demographic and clinical variables between cases and controls

Variables	Levels	Studied groups		P-value
		Case group	Control group	
Age	Mean	53.16	50.48	0.241
Age groups	< 40	10	12	0.412
	40-50	14	21	
	50-60	17	14	
	> 60	21	15	
Sex	Male	31	30	0.875
	Female	31	32	
Fistula location	Cubital	58	51	0.048*
	Wrist	4	11	
DM	Yes	48	40	0.083
	No	14	22	
HTN	Yes	41	37	0.457
	No	21	25	
ESRD	Yes	25	32	0.207
	No	37	30	
Lupus	Yes	3	4	0.697
	No	59	58	
Thrill in the site of fistula	Yes	58	46	0.003*
	No	4	16	

*Statistical significant. DM: Diabetes mellitus; HTN: Hypertension; ESRD: End-stage renal disease

In the patients who had accompanying diseases (diabetes mellitus, hypertension, end-stage renal disease, and collagen vascular diseases), the incidence of fistula thrombosis was less in patients who received ticlopidine, but the difference between the groups of patients with different accompanying diseases was not significant. This shows that the incidence of AV fistula thrombosis does not correlate with the underlying disease, and the difference is because of the drug prescription. In the patients with collagen vascular diseases, fistula thrombosis occurred in none of the patients, but because of the few number of patients in this group, no reliable interpretation can be concluded for this group. Of the 124 fistulas, only 15 of them were in the wrist region, and only one of these (in the placebo-receiving patients) resulted in fistula thrombosis. The number of fistulas in the wrist region is not sufficient to reach a reliable conclusion, and we need other studies to evaluate this type of fistulas.

In the 1- and 3-month follow-ups, no patient had the adverse effects of ticlopidine, and so there was no need to discontinue the drug in any patient. The patients who had fistula thrombosis in their 1-month follow-up were excluded from the study and planned to undergo another surgery to create another AV fistula. After the surgery, they could be included in the study again. In the other studies, Grontoft et al. (13) evaluated the prescription of ticlopidine in AV fistula patients. The incidence of fistula thrombosis in patients who received ticlopidine was 11% and in the placebo group was 47%. There was statistically significant difference between the groups ($P < 0.050$) which shows the effectiveness of ticlopidine.

In another study, Dember et al. (18) evaluated the effect of clopidogrel on patients with AV fistula. The incidence of thrombosis on the patients who received clopidogrel was 12.2%, and in the placebo-receiving group, it was 19.5% ($P = 0.018$). This study concluded that clopidogrel has significant effect on reducing fistula thrombosis incidence after the surgery. Dixon et al. (19) compared two groups of AV fistula patients. In one group, patients received ticlopidine and low-dose aspirin, and in the other group, patients received placebo. Nearly 23% of the patients in the drug-receiving group and 28% of patients in the placebo-receiving group had fistula thrombosis ($P = 0.030$) which showed significant effect of ticlopidine and low-dose aspirin in reducing fistula thrombosis incidence. We recommend more studies with sufficient sample size to evaluate early AV fistula thrombosis and its correlation with fistula region and also collagen vascular diseases. Also, more studies are recommended to evaluate the effect of anticoagulants on dialysis venous catheter and grafts. Aspirin is an inexpensive drug which can be accessed easily, but it has not been studied as much as ticlopidine and clopidogrel, and it can be recommended to study its effects on AV fistula after the surgery.

Based on the finding of this study, due to the significant effect of ticlopidine in reducing the incidence of AV fistula thrombosis, we recommend its prescription after the surgery if there is no contraindication to use it.

Conflict of Interests

Authors have no conflict of interests.

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