



AN INSTITUTIONAL EXPERIENCE ON EFFECT OF CLOPIDOGREL IN PREVENTION OF EARLY FAILURE IN RADIOCEPHALIC ARTERIOVENOUS FISTULA

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ABSTRACT **Context-** the preferred type of vascular access for hemodialysis patient is arteriovenous bypass this is because of lower thrombosis and infection rates and lower health care. The barrier for increased use of AV fistulas in patients treated with hemodialysis is early failure of fistulas due to thrombosis or inadequate maturation. Small, inconclusive trials have suggested that antiplatelet agents may reduce thrombosis of new fistulas. So we have decided to conduct an observational study in our institution on the effect of clopidogrel in preventing failure in patients who had undergone radio-cephalic fistula creation.

Objective- To determine whether clopidogrel reduces early failure of radio-cephalic AV fistulas.

Materials And Methods- Prospective observational study at Madras medical college during the period of 2019-2020. Hundred patients with end-stage renal disease were recruited. Among them 50 patients received clopidogrel and 50 patients not received clopidogrel post-surgery. Each group was followed up till fourteen days after fistula creation.

Outcome Measures- The primary outcome was fistula thrombosis, determined by physical examination at two weeks. The secondary outcome was failure of the fistula to become suitable for dialysis at 6 weeks. Suitability was defined as the fistula flow rate of 300 mL/min or more.

Results- Base line characteristics were statistically not significant in both groups. Fistula thrombosis at fourteen days and failure of fistula to become suitable for dialysis at 6 weeks showed no statistically significant difference in both groups, p value- 0.50 and 0.40 respectively for the outcomes.

Conclusion- Clopidogrel was neither shown to reduce the frequency of early thrombosis of new arteriovenous fistulas at fourteen days post-surgery nor increase the proportion of fistulas that become suitable for dialysis. Larger studies and randomized controlled trials are required in this regard to convincingly determine the role of clopidogrel.

KEYWORDS : clopidogrel, prevention, early failure, radiocephalic fistula

INTRODUCTION

The exact magnitude of the burden of chronic kidney disease or end-stage kidney disease is not known. An Indian population-based study determined the crude and age-adjusted ESRD incidence rates at 151 and 232 per million population, respectively^(1,2). Once an arteriovenous fistula (AVF) is created, it must develop to the point that it is usable. The preferred type of access is a native fistula as AV fistulas have the lowest risk of complications, lowest need for intervention, and the best long-term patency which overall reduces the morbidity and expenditure for the patient. [3] For instance, the annual expenditure associated with VA is more than one billion US dollars in the USA^(4,5).

Vascular access dysfunction is one of the most important causes of morbidity in the hemodialysis population. [6] According to the Japanese Society for Dialysis Therapy (JSDT) guidelines, complications, such as stenosis and thrombosis, cannot be avoided because of prolonged AV use [7]. Primary failure of native fistulas occurs as a result of either thrombosis within the first several weeks following surgical creation (early thrombosis), or inadequate maturation of the vein. [8] The primary AVF failure rate is approximately 9–50%. The clinical manifestations of early fistula failure are failure to develop adequately to permit repetitive cannulation for dialysis, inadequate flow to support dialysis, and thrombosis. The characteristic pathology that results in AVF failure is a juxta-anastomotic stenosis⁽⁹⁾.

However, the advantages of fistulas are counterbalanced by the substantially higher proportion of fistulas than grafts that are never able to be used for dialysis because of failure to mature adequately to support effective hemodialysis.⁽¹⁰⁾ Early fistula failure is the major barrier to increasing fistula prevalence and, in many patients, leads to prolonged use of central venous catheters, which are the least desirable type of vascular access because of their high rates of catheter-associated bacteremia and inadequate solute clearance.

Forearm autogenous arteriovenous (AV) access has been recommended as the first choice for primary access for hemodialysis^{[11],[12]}. The distal radiocephalic arteriovenous fistula (AVF) at wrist is

the gold standard venous access for patients who require long-term hemodialysis as it reduces the risk of steal syndrome compared with elbow fistulas and preserves more proximal vessels for future access placement. However, it has been reported to have a high primary failure rate because of early thrombosis or failure to mature enough to permit adequate dialysis.

Whether primary AVF failure can be prevented with pharmacologic agents has not been extensively examined. Several studies have indicated that the frequency of AVF failure and loss can be reduced with antiplatelet agents.^[13-16] Although those results are encouraging, they do not provide conclusive evidence of the efficacy of antiplatelet agents among patients with AVF. On the basis of these considerations and to further evaluate the effect of platelet inhibition on fistula thrombosis and maturation failure we performed a randomized, placebo-controlled, double-blind trial to find the effect of clopidogrel on the early patency of radiocephalic AV access among patients with ESRD.

MATERIALS AND METHODS

The study is conducted in institute of vascular surgery, medical college from January 2019 to December 2020. The study was a prospective observational study. All patients were subjected to examination of the vessels of both upper limbs including clinical and duplex examination of the veins and arteries.

Inclusion Criteria:

- Age more than 12 yrs
- Life expectancy of at least six months
- Planned creation of native upper extremity Radiocephalic AV fistula

Exclusion Criteria

- The presence of ongoing bleeding or with a history of gastrointestinal bleeding or previous bleeding episodes within six months prior to initiation of the study..
- The presence of a known bleeding disorder (e.g., hemophilia or von Willebrand's disease)

- Patients already receiving anticoagulation therapy or on antiplatelet other than clopidogrel
- platelet count of $<100,000/\text{mm}^3$, and other demonstrated medical conditions that would make antiplatelet therapy dangerous.

Study Design And Procedures

Prospective observational study at Madras medical college during the period of 2019-2020. Between December 2019 and December 2020, 100 patients who met the study criteria were consecutively recruited. Among them 50 patients received clopidogrel and 50 patients not received clopidogrel post surgery. Clopidogrel was administered orally, with a loading dose of 300 mg on day 1 followed by 75 mg each day thereafter for an additional two weeks. Participants receiving clopidogrel was stopped 5 days prior to surgery and was restarted after surgery.

The primary outcome was fistula thrombosis, determined by physical examination at two weeks. The secondary outcome was failure of the fistula to become suitable for dialysis at 6 weeks. Suitability was defined as the fistula flow rate of 300 mL/min or more.

RESULTS

Data was analysed using the statistical program for social sciences (SPSS). None of the patients was lost to follow-up.

Table 1. Baseline Characteristics

Characteristic	Clopidogrel group	Non clopidogrel group	P value
Age (years)	44.23 +/- 3.36	45.8+/-2.84	0.28
Males	20 (40)	30(60)	0.3
Diabetes	22(44)	21(42)	0.46
CAD	7(14)	6(12)	0.76
Bleeding time (Seconds)	415+/-50	435.8+/-60	0.25
Systolic BP	163+/-21.45	154 +/-23.7	0.22

There was no statistically significant difference in baseline characteristics. No severe bleeding episode such as life-threatening bleeding or intracranial hemorrhage was recorded during active treatment period. There were no deaths in either treatment group. Bleeding times were similar at baseline for clopidogrel group (415±50sec) and placebo group (435.8+/-60s).

Table 2. Outcomes

Outcomes	Clopidogrel group	Non clopidogrel group	p Value
PRIMARY OUTCOME			
Fistula thrombosis	4(8)	6 (12)	0.50
SECONDARY OUTCOME			
Failure of fistula to become suitable for dialysis	6 (12)	9(18)	0.40

The primary outcome i.e., fistula thrombosis at 14 days post-surgery was not statistically different among the two groups- 4 patients (8%) in clopidogrel group and 6 patients (12%) in non-clopidogrel group (pvalue-0.50). The secondary outcome i.e, failure of the fistula to become suitable for dialysis was also showed no statistically significant difference between two groups- 6 patients (12%) in clopidogrel group and 9 patients (18 %) in non-clopidogrel group (p Value-0.40)

Table 3. Relationship Of Baseline Variables With Fistula Thrombosis

	Fistula thrombosis	p Value
Age	No significant relationship	0.142
Sex	No significant relationship	0.836
Diabetes mellitus	No significant relationship	0.588
Coronary artery disease	No significant relationship	0.092
Bleeding time	No significant relationship	0.749
Systolic blood pressure	No significant relationship	0.619

The baseline variables showed no significant relationship with fistula thrombosis. There were no deaths attributable to bleeding in either treatment group.

DISCUSSION

In patients with end stage renal disease arteriovenous fistula is the method of choice for the establishment and maintenance of vascular access. Chronic maintenance hemodialysis requires a reliable access. The distal radio-cephalic fistula at wrist is the ideal AVF for

hemodialysis as it reduces the incidence of steal syndrome but with high failure rate. Most of the fistulas fail within three months of surgery. In our institutional experience we have observed that most of fistula thrombosis occurs in first fourteen days. An AVF with primary failure is defined as a fistula that never provided reliable hemodialysis. We conducted a study to determine the effects of clopidogrel on the incidence of early AVF failure among newly created radio-cephalic fistulas. The results of our analysis suggest that daily administration of 75 mg of clopidogrel, beginning from the day of AVF creation for a period of fourteen days was not successful in preventing the development of early vascular failure. We have observed that in terms of absolute numbers, the clopidogrel group has a promising result though it is not statistically significant. The major limitation in our study is the small number of patients and ours is a prospective observational study. But in view of the promising results we believe that our preliminary findings 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. Overall, the effect of antiplatelet agents on vascular access patency needs further investigation. A prospective randomized controlled trial with larger number of patients is warranted in this regard.

CONCLUSION-

Clopidogrel was neither shown to reduce the frequency of early thrombosis of new arteriovenous fistulas at fourteen days post-surgery nor increase the proportion of fistulas that become suitable for dialysis .Larger studies and randomized controlled trials are required in this regard to convincingly determine the role of clopidogrel.

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