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The efficacy of aspirin and dipyridamole on the patency of arteriovenous fistulae and grafts; review of the randomized control trials

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ABSTRACT

Vascular access failure is known as a principal cause of morbidity of end stage renal disease (ESRD) patients. The major reason for vascular access failure is the neointimal hyperplasia which leads to venous thrombosis and stenosis. The efficacy of different pharmacological therapies has been studied in increasing the vascular access patency duration or decreasing the thrombosis of arteriovenous grafts or fistulas. In the current review, we reviewed the results obtained in different randomized control trials considering the efficacy of pharmacotherapy on the thrombosis rate and duration of vascular access grafts patency in HD patients.

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Introduction

The end stage renal disease (ESRD) patients usually undergo renal replacement therapies and hemodialysis, prevalence of which is increasing worldwide. Despite the recent advances in haemodialysis (HD) techniques there is still a considerable mortality rate due to ESRD: almost 220 individual per 1000 patients each year (1). The morbidity and mortality of ESRD patients are mostly associated with the complications related with each type of vascular access (VA) used in hemodialysis which lead to vascular access failure. Different accesses vary considerably in

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terms of the cost, but they have shown almost common complications in patients at different rates.

Vascular access

Using a functional vascular access is a priority in haemodialysis. The three vascular access types commonly used in hemodialysis are arterio-venous graft (AVG), arterio-venous fistula (AVF), and cuffed central venous catheter (CVC) (2). Using native mature AVF is known as the gold standard method especially in Europe that accounts for almost 80% of the accesses. Increasing the blood flow, dialysis advancement, higher stability, lower risk of infection, clotting, and surgical interventions requirement are properties which increase the AVF reputations among other available methods. Depending on age, sex, body mass index (BMI), availability of appropriate vascular path, disease conditions (such as obesity, diabetic type 2, and peripheral vascular diseases), and failing to mature of fistula, A-V graft or central venous catheters will be the preferred VA (3). A-V Graft; created by a synthetic tube connecting a vein to an artery, and central venous catheters; associated with inadequate solute clearance, have been commonly used in the United States. Based on different studies the patency rate of AVG can be observed as low as 23% (even 4% in some reports) each year (4-6).

Early referral of ESRD patients to nephrologists, vein maintenance, performing microsurgery, providing a skillful dialysis team, and vessel mapping for detecting the best access site, diagnosis of thrombosis and stenosis of the vein are simple issues which can improve the dialysis consequences, VA survival rate, and decrease the complications (7-9). The VA failure is the most important cause of mortality, morbidity, and vascular access elimination or substitution in HD patients (10). Therefore constructing a stable, functional VA to supply the adequate blood flow for HD and decrease the complications, is indispensable and vital for better HD performance in ESRD patients.

Vascular access complications

Several complications may result in vascular access loss such as infections, sepsis, thrombosis, aneurysm, stenoses, and ischemic events which lead to access loss, more hospitalization, and further costly surgical interventions requirement to restore the access patency. Catheters are highly susceptible to infections, bacteremia, and thrombosis and are better to be applied as temporary accesses in exceptional situations. Grafts are prone to stenosis and thrombosis. Thrombosed grafts necessitate more surgical approaches such as thrombectomy and angioplasty (11).

According to the previous published literature, thrombosis of artery and vein is the major complication in HD patients, which is the major cause of vascular access loss and mortality among end stage renal disease patients (ESRD) (12). Various thrombotic abnormalities have been detected in ESRD patients. Platelet activation commonly occurs in ESRD patients due to various stimuli. Increase of P-selectin, glycoprotein 53, activated fibrinogen receptor-1, and serum fibrinogen, have been observed in a study of Greaves K, et al, which were among platelet factors in thrombosis. Increase in the number of platelets receptors (glycoprotein IIb/IIIa and glycoprotein Ib) may also lead to thrombosis in ESRD patients (13,14).

The hemodialysis procedure and the artificial circuit themselves, stimulate platelet activation by exerting shear stress and turbulence in the VA and vascular accesses facilitate fibrinogen adhesion to platelet. Inflammatory factors; cytokines tumor necrosis factor-a and interleukin-6, and extrinsic factors; uremic toxins, anemia,

hyper-homocysteinemia, oxidative milieu, and abnormalities of von Willebrand factor, all promote the risk of thrombosis in ESRD patients (15-17).

Intimal hyperplasia; which is resulted from tissue oxidative stresses, platelet derived growth factor, vascular smooth muscles and myofibroblasts proliferation, leads to stenosis and lowers blood flow which eventually increases the possibility of hypercoaguability, clot formation, hypotension, and hypovolemia (14,18). Concentration changes of some plasma factors may also contribute in thrombosis events, which are detailed in Table 1.

Table1. Plasma factors contributing to thrombosis in ESRD patients

Increased level	Decreased level
d-dimers	Protein C anticoagulant activity
Prothrombin fragments 1+2	Antithrombin III
Thrombin-antithrombin complex	Protein S
Tissue factor	Albumin
Antiphospholipid anti-bodies	
Plasmin-antiplasmin complex	

Pharmacological therapies

Although there are some investigations about drugs efficacies on function and patency time of vascular accesses, mortality, bleeding, etc. there is no definite or specific pharmacological interventions with risk reduction effect on thrombosis complication in HD patients.

Since 1996, pharmacotherapy approaches and drug including angiotensin II inhibitors, nonsteroidal anti-inflammatory drugs, coagulation modifiers, calcium channel blockers, antiplatelet agents, coumarins, and heparins have been used for prevention of thrombosis in ESRD patients (19).

Ticlopidine, aspirin, dipyridimole, clopidogrel, and sulfinpyrazone are examples of anti-platelet drugs used in randomized control trials to examine their effects on vascular access patency and thrombosis.

Dipyridamole is a phosphodiesterase inhibitor with vascular anti-proliferative and vasodilation activities which restrain the platelet activation through potentiating of adenosine mechanisms, reducing the adherence of platelet to the vessels wall and selectively decrease the platelet derived growth factor serum level. This is a specific characteristic of the dipyridamole and no antiplatelet drugs have this property (20-22).

Aspirin (acetylsalicylic acid); a non-steroidal anti-inflammatory drug and COX inhibitor, implicates anti-thrombotic effects by acetylation of the platelet cyclooxygenase (COX) at the site of amino acid serine 529 and lead to inhibition of platelet-dependent thromboxane A2 formation in an irreversible manner. The dosage of administered aspirin determines its effect as a potent inhibitor of COX 1; with anti –thrombotic effects, or the inhibitor of COX2; with anti-inflammatory effects. Due to bleeding risk reported as a side effect of aspirin, the optimum dose for aspirin application is obtained by considering the benefit/risk ratio of individuals (23). Aspirin can reduce the platelet activation through interfering in different mechanisms such as nitric oxide (NO)/cGMP-dependent process and increasing the NO production in endothelial cells (24,25).

Ticlodipine and clopidogrel are ADP receptor/P2Y12 inhibitors from the thienopyridine family which have platelet inhibitory properties. These platelet surface receptors are involved in glycoprotein IIb/IIIa receptor activation. These drugs have preventive effects on ADP-induced platelet aggregation not directly on arachidonic acid metabolism (26).

Sulfinpyrazone is among drugs which might prevent thrombosis mostly in combination with other anti coagulants, but there is not certain conclusions about the mechanism of sulfinpyrazone interfering (27).

Fish oil, is an omega 3 fatty acid which affects the platelet aggregation by reducing thromboxane A2 synthesis through limiting the availability of arachidonic acid. It is usually used in combination with aspirin (28).

RCTs on the efficacy of aspirin, dipyridamole, and warfarin

Dipyridamole, aspirin (Acetylsalicylic Acid), and warfarin are three common drugs evaluated (separately or in combination) in a few randomized controlled trials (RCT) regarding their effects on VA thrombosis and patency rate. Detailed data of these trials are summarized in Table 2.

Besides the application of aspirin in post surgical situations, its efficacy in inhibiting hyperplasia is still under debate. According to in-vitro examinations aspirin increased the proliferation of platelet derived growth factor induced vascular smooth cells. This was in accordance with the study of Sreedhara et al., that observed an increased thrombosis rate in patients treated with aspirin alone (50%) compared with the groups who received no pharmacological treatment, treated only with dipyridamole (17%), and even treated with the combination of dipyridamole and aspirin (23%) (29). According to the Sreedhara et al., by using dipyridamole alone or in combination with aspirin a reduction in the thrombosis rate and vascular access patency (more than 70%) have been observed in patients with primary AVG. Administered dipyridamole alone or dipyridamole plus aspirin did not show any beneficial effects on patency duration of secondary AVG. The results obtained in the study of Sreedhara et al. were not statistically significant; which might be due to low number of patients. It is suggested that applying the combination of low doses aspirin with dipyridamole can be more beneficial than the aspirin alone (29,30).

In another RCT by Bradley et al. extended release dipyridamole plus low dose aspirin (ERDP/ASA) had a significant but modest effect on increasing the duration of primary A-V graft patency and reducing the vascular stenosis. The authors in Bradley et al. study believed that for parimary A-V grafts dipyridamole with or without aspirin would be more effective in regulating the stenosis and access patency (31).

Results of some studies were in contrast with Sreedhara, et al. about the efficacy of aspirin, and have proposed that aspirin has considerable anti-platelet activity. They proposed that using low doses of aspirin is associated with the decreased platelet adhesiveness, thrombosis incidence of A-V fistula or graft, and increased patency duration of primary A-V graft, but not the mortality rate and cumulative A-V graft patency (32,33).

Aspirin administration to patients with uremic manifestation and abnormal platelet function was associated with gastrointestinal bleeding. Harter in 1979 showed that low dose of aspirin (160 mg per day) is the optimum dosage in men which reduces the risk of thrombosis (32,33). Cardiac events, gastrointestinal bleeding, headache, nausea, and vomiting are different adverse effects observed in patient receiving dipyridamole and aspirin (separately or in combination), which might be due to patient's prior history of the observed side effects or high dosage of the drugs.

Using warfarin which was examined by Crowther, not only showed no beneficial effect on A-V graft failure but also patients were at high risk of hemorrhage (gastrointestinal bleeding, cerebral haemotoma, and femoral artery injury) (34). Crowther et al. mentioned that although vascular access

failure did not improved by using warfarin, the time of graft loss was increased in patients. This trial was stopped due to severe side effects. The possibility of warfarin efficacy in reducing early graft loss needs to be more investigated (34).

As shown in Table 2, different RCTs showed discrepant results. This can be due to heterogeneity among studies.

For example, the patency duration of A-V grafts and fistula following administrating different pharmacotherapies was evaluated by detecting the presence of thrombosis, through mechanisms such as touching and using stethoscope, dialysis needle, doppler technique, physical removal of thrombosis,

Table 2. Characteristics of the RCTs

Author Year Reference	Country	Interventions, participants	Evaluated outcomes	Major results
Andrassy 1974 (32)	Germany	Aspirin 1gr (500 mg pd) vs. placebo 1 month follow up Male=50, Female=42	Primary Fistula Thrombosis	Thrombosis In aspirin arm: 2/45 In placebo arm: 11/47 OR: 0.15 95% CI (0.03 to 0.73)
Harter 1979 (33)	United State	Aspirin 160 mg (1pd) vs. placebo 5 months follow up	Primary Graft Thrombosis	Thrombosis In aspirin arm: 6/19 In placebo arm: 18/25 OR: 0.18 95% CI (0.05 to 0.66)
Sreedhara 1994 (29)	United State	1-Aspirin 325 mg qd with Dipyridamole placebo 3 pd 2-Dipyridamole 75 mg 3 pd with aspirin placebo 1 pd 3-Dipyridamole 75 mg 3 pd with aspirin 325 mg pd	Primary Graft Thrombosis	Thrombosis in 1- Aspirin arm: 10/19 vs. placebo arm: 6/18 OR: 2.22 95% CI (0.59 to 8.41) 2- Dipyridamole arm vs. placebo: OR:0.57 95% CI (0.13 to 2.51). 3- (Dipyridamole+Aspirin) arm: 6/18 vs. Placebo arm: 6/18 OR: 0.77 95% CI (0.19 to 3.19)
Bradley 2009 (31)	United State	Dipyridamole+Aspirin (ERDP/ASA)* 200 mg+25 mg, (2 pd)	Primary AVG Thrombosis & Loss of primary unassisted patency	Loss of primary unassisted patency: (ERDP/ASA): 256/321 vs. placebo: 274/328 HR**:0.82 95% CI: (0.68–0.98) Thrombosis: (ERDP/ASA):127/321 vs. placebo: 139/328 HR: 0.84 95% CI:(0.65–1.08)
Crowther 2002 (34)	Canada	Warfarin variable dose with target INR 1.4-1.9 Follow up: 37months Warfarin n: 56 Placebo n: 51 Sex: M=61, F=46	Primary graft thrombosis	Thrombosis Warfarin arm vs. placebo arm OR: 1.76 95% CI (0.72 to 4.34)

*ERDP/ASA: Extended release dipyridamole plus low dose aspirin; **HR: Hazard Ratio;

edema, and ease of cannulation (29,32,33, 35). Duration of drug exposure, dosage, mechanism of delivery, and number of examined patients differs in the RCTs mentioned in Table 2 and can contribute to the discrepant findings.

Conclusion

according to the RCTs reviewed in the current study, administrating drugs such as aspirin and dipyradimole or their combination, may result in beneficial effects regarding vascular access longevity for short term duration in ESRD. However, there is not any certain conclusion on the effects of long-term pharmacotherapy of ESRD patients with AVG or AVF. It is not obvious whether the combination of dipyridamole and aspirin will be more effective than aspirin alone on the graft patency.

Due to noticeable discrepancy among RCTs mentioned in our review, there is a need for more investigations on the efficacy of pharmacological agents such as aspirin, in improving the vascular access patency.

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Conflict of Interest

The authors declare no conflict of interest.

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