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Case Study *Open Access*

A comparative N-of-1 study trial of aspirin Vs clopidogrel in the treatment of peripheral artery disease – A case report

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ABSTRACT

N-of-1 or single subject clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions. Aim and objective: The main aim of the study is to compare the efficiency of 2 antiplatelet drugs, Aspirin 81 mg (drug-A) and Clopidogrel 75 mg (drug-B), as N-of-1 trial in the treatment of peripheral artery disease. Method: Single patient N-of-1 Trial. A 4week study period was selected for each drug therapy, in order to allow each treatment an adequate time to manifest its clinical effects. A washout period of 1 week was used between the two drug therapies to eliminate or reduce the carryover effect of the treatment used in the previous time period. Results: The study shows that Clopidogrel (drug-B) was found clinically effective than aspirin in peripheral artery disease. Discussion: Clopidogrel (Drug-B) directly inhibits platelet adhesion, whereas aspirin inhibits only secondary activation of platelets. Conclusion: It was found that Clopidogrel (drug-B) treatment has potent efficiency in patients with symptomatic peripheral artery disease in compared with aspirin in preventing ischemic events.

Keywords: Peripheral artery disease, N-of -1 trial, Aspirin, Clopidogrel, Antiplatelets

INTRODUCTION

Peripheral artery disease (PAD) is a chronic, atherosclerotic disease of the peripheral vasculature resulting in limb-associated complications such as intermittent claudication, ischemic rest pain, ischemic ulcer, gangrene, and functional impairment. [1] PAD is also a major risk factor for heart attack, stroke and cardiovascular death. The incidence of PAD varies in the general population with 15–20% in people older than 70 years. [2] Approximately 50% of patients with PAD have atypical lower-extremity symptoms and 40% are asymptomatic. [3] However, all patients with PAD, whether classic ischemic leg symptoms are present or not, have limited physical activity, impaired walking speed and endurance, and functional decline. Left untreated, PAD can lead to limb amputation. [4]

PATHOPHYSIOLOGY AND RISK FACTORS OF PAD

PAD results from any disease causing stenosis or occlusion of the lower limb arteries with atherosclerosis disease being the most common aetiology. The risk and incidence of peripheral artery disease is higher than coronary artery disease and other vascular disease due to limited supply of blood to lower extremity compared to other organs. In the pathophysiology of atherothrombosis of PAD, endothelial layer is damaged followed by impaired platelet function. [5] Platelet adhesion, activation and aggregation occurs immediately after disruption of endothelium. Adhesion occurs through binding of Von Willebrand's factor and glycoprotein receptor along with receptors of fibronectin and collagen. Adhesion leads to activation with liberation of variety of cytoplasmic granules including ADP, TXA2, collagen, serotonin, epinephrine and thrombin. [6]

Studies have confirmed that risk factors for cerebrovascular disease and ischemic heart disease, such as age, gender, obesity, diabetes, hypertension, smoking, and hyperlipidaemia are involved in 80%-90% of peripheral artery disease. [7]

METHOD: N-OF -1 TRIAL

An N of 1 trial is a clinical trial in which a single patient is the entire trial - a single case study. N-of-1 trials are a specific form of randomized or balanced designs characterized by periodic switching from active treatment to placebo or between active treatments.

N-of-1 trials use crossover between treatments to address the problem of patient-by-treatment interaction. This situation arises when characteristics of the individual affect whether treatment A or treatment B (which could be an active treatment, a placebo, or no treatment) delivers superior results. [8]

Single-patient trials may be poised to emerge as an important part of the methodological armamentarium for comparative effectiveness research and patient-centered outcomes research. By permitting direct estimation of individual treatment effects, they can facilitate finely graded individualized care, enhance therapeutic precision, improve patient outcomes, and reduce costs. [9]

Study for comparative n-of-1 trial of aspirin vs clopidogrel in peripheral artery disease (pad)

Tab: 1 Subject demographic details

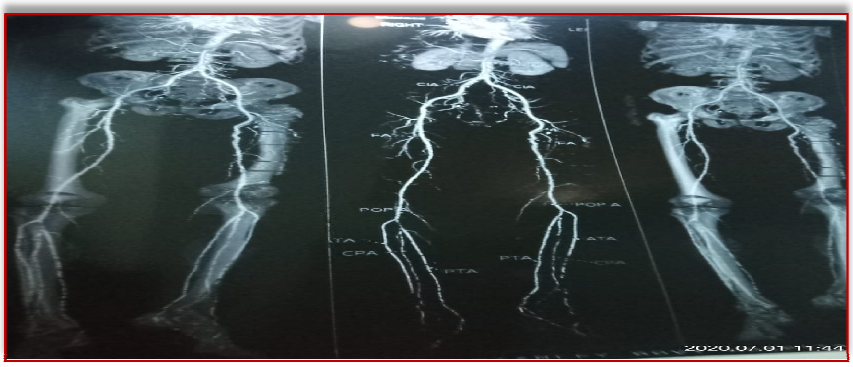
Patient Name	Mr.X
Age /Gender	63/Male
Weight	50kg
On examination	Conscious and oriented
Vitals	
Heart rate	75 breaths per minute
Breathingsound	BAE +
Heart sound	S1S2 +
Past medical history	Diabetes milletes (DM)-1for15 years, Tuberculosis(TB) for 3 months Major surgery on acetabulum of left leg before 7 years, PAD for 1 year.
Past medication	Human mixtard- (30/70) 40 IU 0-0-1 (15units) , Metformin -500mg 1-0-1, Anti-tubercular treatment (ATT) – 4 drug regiment Pyridoxin 40mg 1-0-0, Aspirin 81mg 0-0-1
Study for	Comparative trial of Aspirin vs Clopidogrel in PAD

CLINICAL ASSESSMENT

Leg numbness, difficulty in walking (patient become bed ridden), painless sores on toes, pain on leg.

LABORATORY INVESTIGATION FOR PERIPHERAL ARTERY DISEASE (PAD)

Angiogram: The atherosclerotic plaque and narrowing of the tibial artery in left leg (image 1}



(**Image:1 - atherosclerotic plaque and narrowing of the tibial artery in left leg)**

TREATMENTPATTERN

The unit of treatment assignment is a pre-specified time period, say 4 weeks, during which the patient receives either treatment A or B.

The duration of the treatment period is selected to allow each treatment an adequate time to manifest its effect.

A washout period might be used between the two treatment periods to eliminate or reduce the carryover effect of the treatment used in the previous time period.

Drug A – Aspirin 81 mg 1-0-1 (Duration:02/11/2020-29/11/2020) - 4 weeks

Washout period – 30/11/2020- 06/12/2020 (1 week)

Drug B – Clopidogrel 75 mg 0-0-1 (Duration: 07/12/2020-03/01/21) -4 weeks

RESULTS

Parameters	Aspirin	Clopidogrel
Clinical assessment	Still difficulty in walking Decrease in pain scale	Patient feels free to move leg on day 3 and started walking at end of treatment.
Interaction	-	-
Llight transmission aggregometry (LTA) results interpretation Agonist-ADP (Platelet aggregation)	52%	63%

DISCUSSION

In pathophysiology of atherothrombosis of PAD, following the damage of endothelium platelet event occurs. Platelet adhesion, activation, and ultimately aggregation occur immediately following disruption of the endothelium. Francisco J Serrano Hernando etal ., in their study stated the chronological events of atherothrombosis in the pathophysiologic of PAD. [10] Platelet adhesion occurs through binding of von Willebrand's factor and glycoprotein (GP) receptors, along with receptors for fibronectin and collagen. Platelet adhesion leads to activation of the platelet with the liberation of a variety of cytoplasmic granules including adenosine diphosphate (ADP), thromboxane A2 (TXA2), collagen, serotonin, epinephrine, and thrombin. [10]

The blood vessel supplying lower extremities is generally reduced in PAD comparative to blood vessel supplying highly perfused organs. So, adhesion of platelet is play important role than the activation of surrounding platelet via TXA2 as there is reduced platelet normally compared to larger blood vessels. So, it important to block the platelet adhesion rather platelet activation i.e., the inhibition of platelet adhesion completely block the mass of platelet plug where the inhibition of TXA2 allow some platelet mass which is formed by primary platelet adhesion. Especially in PAD platelet mass is mainly due to platelet adhesion than platelet activation. [11]

CLOPIDOGREL - MECHANISM OF ACTION

The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP- mediated activation of the glycoprotein GPIIb/IIIa complex,thereby inhibiting platelet aggregation. This action is irreversible. [12] (Figure 1).

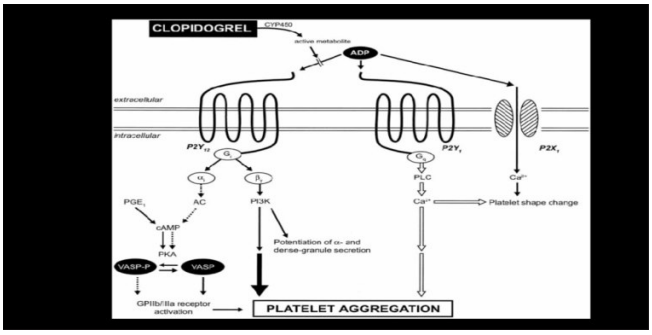


Fig: 1. inhibition of platelet aggregation by Clopidogrel

ASPIRIN - MECHANISM OF ACTION

Aspirin (acetylsalicylic acid) irreversibly inhibits prostaglandin H synthase (cyclooxygenase-1) in platelets and megakaryocytes, and thereby blocks the formation of thromboxane A2 (TXA2; a potent vasoconstrictor and platelet aggregate) Aspirin as an antiplatelet drug. [13] (Figure 2).

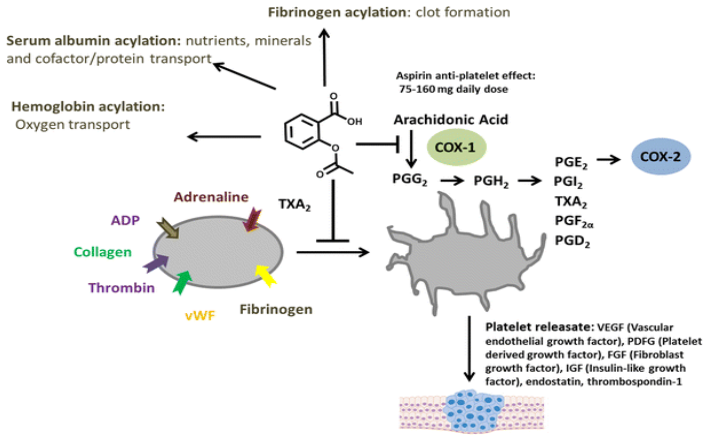


Fig: 2. Antiplatelet activity of Aspirin.12

As we discussed earlier, since clopidogrel directly inhibits platelet adhesion, clopidogrel it is considered to be more effective than aspirin.

CONCLUSION

From the Study of n-of-1 trail the subject is involved in study was not an aspirin resistant which was found from the results of LTA diagnosis (agonist-ADP), it was found that Clopidogrel (P2Y12

receptor blocker) treatment in patients with symptomatic PAD was more effective than aspirin (Thromboxane A2 synthesis inhibitor) in preventing ischemic events. The drug clopidogrel also allows single dosing, which increases the patient compliance.

REFRENCES

[1]. Graham H. Bevan, Khendi T. White Solaru, Evidence-Based Medical Management of Peripheral Artery Disease, Arteriosclerosis, Thrombosis, and Vascular Biology, 40(3), 2020, 541-5

[2]. P. Abdulhannan, D. A. Russell, S. Homer-Vanniasinkam, Peripheral arterial disease: a literature review, British Medical Bulletin, 104(1), 2012, 21–39

[3]. Schirmang T, Ahn SH, Murphy TP, et al. Peripheral arterial disease: update of overview and treatment, Med Health R, 92, 2009, 398-402.

[4]. Hirsch, AT, Haskal, ZJ, et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic) AHA journals, Circulation 2006, 113:e463

[5]. Flu HC,Tamsma J, Lindeman JHN, et al. A systematic review of implementation of established recommended secondary prevention measures in patients with PAOD, Eur J VascEndovasc Sur, 39, 2010, 70-86

[6]. Francisco J Serrano Hernandoa, Antonio Martín Conejeroa Peripheral Artery Disease: Pathophysiology, Diagnosis and Treatment, Rev EspCardiol. 60(9), 2007, 969-82,

[7]. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Prevalence of conventional risk factors in patients with coronary heart disease, JAMA, 290, 2003, 898-904

[8]. Kravitz RL, Niedzinski EJ, Hay MC, Subramanian SK, Weisner TS. What ever happened to N-of-1 trials? Insiders' perspectives and a look to the future. Milbank Q, 86(4), 2008, 533-555.

[9]. NaihuaDuana Richard L.Kravitzb Christopher H.Schmidc Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness Journal of Clinical Epidemiology, 66(8), Supplement, 2013, S21-S28

[10]. Francisco J. Serrano Hernando and Antonio Martín Conejero, Peripheral Artery Disease: Pathophysiology, Diagnosis, and Treatment, Rev EspCardiol, 60(9), 2007, 969-82

[11]. John P Cooke, The pathophysiology of peripheral arterial disease: rational targets for drug intervention, Vascular Medicine, 2, 1997, 227-230

[12]. Kallirroi I Kalantzi, Maria E Tsoumani; Ioannis A Goudevenos; Alexandros D Tselepis. Pharmacodynamic Properties of Antiplatelet Agents, Expert Rev ClinPharmacol, 5(3), 2012, 319-336.

[13]. Ornelas, A., Zacharias-Millward, N., Menter, D.G. et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. Cancer Metastasis Rev 36, 2017, 289–303. https://doi.org/10.1007/s10555-017-9675-z