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A REVIEW ON BENEFICIAL EFFECTS OF DUAL ANTI-PLATELET THERAPY FOR TIA

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Abstract: **Aspirin with clopidogrel is a standard therapy for acute coronary syndrome and percutaneous coronary intervention. DAPT (dual antiplatelet therapy) effectively inhibit platelet activation and reduce ischemic stroke compared to antiplatelet monotherapy. However, DAPT carries an increased risk of bleeding like intracranial haemorrhage. The use of DAPT over long term determines the major systemic bleeding events. Physicians should assess benefits and risk with DAPT over monotherapy in ischemic stroke patients.**

Keywords: **aspirin, clopidogrel, dual antiplatelet therapy, ischemic stroke.**

1. INTRODUCTION

Platelet is one of the blood components; the main function is to stop the bleeding injuries [1]. Platelets have no cell nucleus; they are fragments of cytoplasm from the megakaryocytes [2] of bone marrow and the entire circulation. These inactivated platelets are bio convex [3,4] discoid structures with 2-3 µm in diameter. Coronary heart disease is defined as disease which is a waxy substance called plaque builds up inside the coronary arteries; these arteries supply oxygen rich blood to the heart muscle. When plaque builds up in the arteries, the condition is called atherosclerosis and build-up of plaque occurs over several years. It is defined as the sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain. There are two types of stroke namely ischaemic stroke and haemorrhagic stroke. Ischaemic stroke is similar to the heart attack, except it occurs in the blood vessels leading to the brain. These clot block blood flow to the brain cell. Ischaemic stroke can also occur when too much plaque clogs the brains blood vessels. About 80% of the strokes are ischaemic. On the other hand haemorrhagic stroke occurs when a blood vessel in the brain breaks or ruptures. The most common cause of haemorrhagic stroke is high blood pressure and brain aneurysms. Aneurysms are a weakness or thickness in the blood vessel wall. The aim of the study was related to the effectiveness of using dual antiplatelet therapy in coronary heart disease.

2. EPIDEMIOLOGY

Epidemiology of stroke

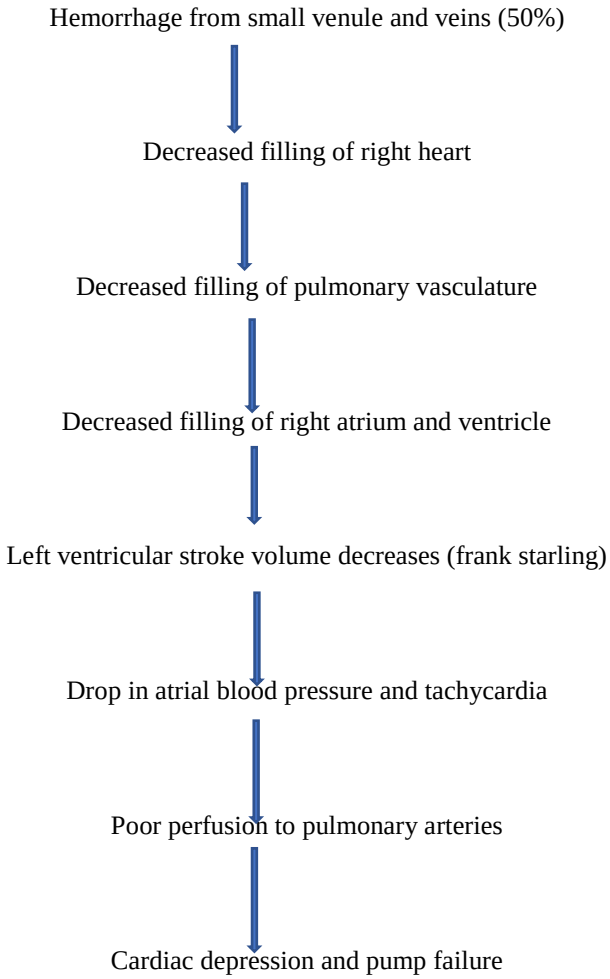
In Kolkata [5] a study made from 1998 to 1999 showed a prevalence rate of 147/100,000 and an annual incidence rate of 36/100,000. When adjusted to the 1996 US population, the age adjusted prevalence rate was 334/100,000 and the age adjusted annual incidence rate was 105/100,000. Compared to men, women had substantially higher age adjusted prevalence rate of 564/100,000 for women and 196/100,000 for men and incidence rate of 204/100,000 for women versus 36/100,000 for men. For all age groups except for people aged 50-69 years, women had a higher prevalence rate than men. Among stroke patient who underwent neuroimaging study (59.5% of all stroke) 68% proved to be infarct and the remaining 32% to be haemorrhage [6]. The prevalence of stroke in India shows a huge variation of 147-922/100,000 across diverse community-based studies [7]. In several studies which used age standardization with US population as reference, the prevalence of stroke ranged from 244/100,000 to 424/100,000. According to the India stroke factsheet updated inn

2012, the estimated age adjusted prevalence rate of stroke ranges between 84/100,000 and 262/100,000 in rural and between 334/100,000 and 424/100,000 in urban areas. More than 100000 Korean people experience a new or recurrent stroke [8]. Approximately 62000 Canadians suffer of stroke or TIA each year, ischemic stroke currents accounts for more than 75% of all strokes is a recurrent stroke [8,9].

EPIDEMIOLOGY OF CORONARY HEART DISEASE

Coronary heart disease (CHD) is the most common cause of death in the UK. 1 in 5 men and 1 in 7 women die from CHD. There are 80,000 deaths from CHD in the UK each year. Death rates from CHD are highest in Scotland and the north of England and the lowest in the south of England. Death from CHD is more likely during winter and is increased winter mortality increases with increasing age. In recent years, CHD death rates have been falling more slowly in younger age groups and fastest in those aged 55 and over. There is some evidence that these rates are beginning to level off in younger age groups. Death rates from all heart attacks and heart attack that are immediately fatal have declined, with around 50% decrease in men and women since 2002 and 2010. Despite the decline in death rates from cardiovascular disease (CVD) in the UK, rates are still relatively high compared to other western European countries [10]. In Western Europe only Ireland, Germany, Sweden and Luxembourg had a higher death rate than the UK in the same year. The overall incidence of myocardial infraction in England in 2010 was 154 per 1000,000 in women. The overall incidence of myocardial infraction in Scotland in2009 was per 1000,000 in men and 113 per 100,000 in women.

PATHOPHYSIOLOGY:



RELATIONSHIP BETWEEN STROKE AND CHD

Several types of heart disease are risk factors. Likewise, stroke is risk factors for coronary heart disease. Coronary heart disease and stroke share many of the same risk factors such as high LDL (bad) cholesterol level, low HDL (good) cholesterol level, high blood pressure, smoking, diabetes, physical inactivity and being overweight or obese.

Individuals with coronary heart disease, angina or who have had heart attack due to atherosclerosis, have more than twice the risk of stroke than those who haven't. If you have atherosclerosis in the coronary arteries you are very likely to have atherosclerosis in other parts of your body.

3. DRUG OF CHOICE FOR DUAL ANTIPLATELET THERAPY

Aspirin (antiplatelet)

Taking aspirin has both potential health benefits and possible risks of bleeding. Daily aspirin therapy reduces risk of subsequent heart attacks in patient with prior history of a heart attack, coronary artery disease (like atherosclerosis) or risk factors for developing coronary artery disease. Aspirin is used for prophylaxis TIA and stroke except in patient with an allergy to aspirin or salicylates.

- The mechanism of action for aspirin stroke prevention is the inhibition of prostaglandins synthesis action to prevent the formation of platelet aggregate substance thromboxaneA2.
- The usual dose for indication in adults 50-325mg/day. Aspirin should be taken with food, milk or large glass of water to decrease GI problem. Monitor for signs of bleeding.
- The side effects of stroke are caused by a burst blood vessel. While daily aspirin can help prevent a clot related stroke, it may increase your risk of a bleeding stroke (haemorrhagic stroke)
- Gastro intestinal bleeding
- Allergic reaction
- The lack of blood to areas of heart is the main cause of heart attack. The lack of blood to areas of the brain is one cause of stroke. Aspirin can increase the risk of bleeding in the stomach, small intestine and brain. If aspirin is taken at high doses and for a long time, it can slowly damage this layer.

Limitation of aspirin

- Not for use as initial dose of aspirin therapy during onset of acute coronary syndrome, acute myocardial infraction or before PCI
- Not shown to reduce the risk of GI bleeding due to aspirin

Clopidogrel (antiplatelet)

Clopidogrel is used to prevent heart attacks and stroke in persons with heart disease, recent stroke or blood circulation disease. It is also used with aspirin to treat new/worsening chest pain (new heart attack, unstable angina) and to keep blood vessel open.

- Drug mechanism it blocks the adenosine phosphate receptors which prevents fibrinogen binding to the receptor. This decrease the ability of platelet addition and aggregation.
- The usual dose for stroke prevention in 75mg once a day and can be taken without food. It may be used as alternative to aspirin containing products in patient's allergy to aspirin or salicylates.
- The side effects are severs bleeding or pain, vomiting with blood, weakness or numbness in an arm or leg, blood in your pee or blood in your poo, an allergic reaction this can cause a sudden, itchy rash, swelling of the lips, mouth or throat and breathing problems.

Limitations of clopidogrel

- Slow onset
- Low level of inhibition
- Too much variability

CLOPIDOGREL AND ASPIRIN

- The combination of clopidogrel and aspirin is used to reduce future atherosclerosis events in patients with the recent stroke or the patients who had stroke while on clopidogrel

- The mechanism of action for each drug is different. Clopidogrel blocks the adenosine phosphate receptor which prevents fibrinogen binding to the receptor while aspirin inhibits prostaglandins synthesis action to prevent the formation of platelet aggregation.

DUAL THERAPY FOR PATIENTS WITH ACUTE ISCHEMIC STROKE OR TIA

Keun-sik Hong *et al.*, proved that the benefits of dual therapy with clopidogrel plus aspirin in patients with acute coronary syndrome (ACE) and percutaneous coronary intervention (PCI) has been well established in multiple large clinical trials [11-16] compared to aspirin monotherapy, clopidogrel plus aspirin has been shown to reduce the risk of the composite of vascular events at the cost of more major bleeding events over variable periods from 8 days to 12 months. It should be noted that these trials exclusively included the following types of patients who were in the high risk periods patient experiencing ST elevation myocardial infraction (STEMI), acute coronary syndrome (ACE) with non- STEMI, or suspected acute myocardial infraction (MI) within 12-24 hours of onset or patient with symptomatic CHD who were highly likely to undergo elective PCI. In addition, the duration of dual antiplatelet therapy was ≤12 months. Therefore, the benefits and harm of dual antiplatelet therapy observed in patient with ACS or those undergoing PCI are not directly applicable to long term dual antiplatelet therapy for patients with ischemic stroke or TIA.

Short term Dual antiplatelet therapy for patients with acute ischemic stroke and TIA

In two small trials clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) and clopidogrel plus aspirin for infraction reduction in acute stroke or transient ischemic attack patient with large artery stenosis and micro embolic signals (CLAIR), clopidogrel plus aspirin was found to be more effective than aspirin monotherapy for preventing the asymptomatic micro embolic signals detected by trans cranial doopler ultrasound. However, these two trials were proof of concept studies using surrogate markers and thus did not have adequate statistical power to demonstrate the clinical efficacy of reducing stroke or TIA with clopidogrel plus aspirin dual therapy.

The largest trial was the clopidogrel in high risk patients with acute non disabling cerebrovascular events (CHANCE) trial, which compared clopidogrel plus aspirin versus aspirin monotherapy in 5170 patients with minor ischemic stroke. The rate of the primary endpoint of a recurrent stroke within 90 days was significantly lower for dual therapy than for aspirin monotherapy. The rate of composite events including stroke, MI or vascular death was also lower with dual therapy than with aspirin monotherapy. A particularly notable finding was than the rate of moderate or severe bleeding did not differ between the two groups.

Clopidogrel in high risk patient with acute non disabling cerebrovascular event was a pivotal trial for the following reasons:

- It was the first large trial of dual therapy focusing on patient with TIA and minor ischemic stroke who are at high risk of recurrent ischemic stroke and at low risk of intracranial bleeding

- It tested a short course of dual antiplatelet therapy, thereby maximizing the efficacy and minimizing the risk

- It demonstrated a substantial treatment effect with a number needed to treat of 29 for preventing one recurrent stroke. However, it should be noted that the results of both the clopidogrel in high risk of patients with acute non disabling cerebrovascular events and platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trials will be directly applicable to patient with minor stroke or high-risk TIA presenting within 12-24 hours.

Long term clopidogrel plus aspirin therapy in patient with ischemic stroke or TIA

The first large trial was the management of atherosclerosis with clopidogrel monotherpy in high risk patient with recent TIA or ischemic stroke (MATCH) study, which was a randomized, double blind, placebo controlled trial to compare clopidogrel 75mg once daily plus aspirin 75mg once daily versus clopidogrel monotherapy in patients who had an ischemic stroke, previous MI, angina pectoris, diabetes mellitus or symptomatic peripheral arterial disease (PAD). The management of atherosclerosis with clopidogrel in high risk patient with recent TIA or ischemic stroke (MATCH) trial includes the clopidogrel plus aspirin group and the clopidogrel monotherapy group had similar rates for the primary efficacy endpoint of the composite of ischemic stroke, MI, vascular death or hospitalization for TIA, angina pectoris or

worsening of PAD. However, the dual therapy group had significantly more major bleeding events. Therefore, adding aspirin to clopidogrel provided no further benefit, while increasing the harm.

The clopidogrel for high atherosclerosis risk and ischemic stabilization, management and avoidance trial were another large randomized, double blind, placebo-controlled trial which compared clopidogrel 75mg once daily plus aspirin 72-162 mg once daily versus aspirin monotherapy in 15603 patients with established cardiovascular disease or with multiple risk factors. The trial revealed no significant benefit of adding clopidogrel to aspirin during the 2 months follow up for preventing the composite of vascular events in this broad population of patients at high risk for atherosclerosis events [17].

The most recent trial was the secondary prevention of small subcortical strokes (SPS3) trial, which was a randomized, double blind, placebo controlled trial that compared clopidogrel 75 mg once daily plus aspirin 325 mg once daily versus aspirin monotherapy in 3020 patients who had a symptomatic lacunar infraction confirmed by magnetic resonance imaging within 6 month of onset, with a mean follow up of 3.4 years. The rate of primary endpoint of recurrent stroke did not differ between the clopidogrel plus aspirin group and the aspirin monotherapy group. There was no difference between dual therapy and aspirin monotherapy in the rate than the aspirin monotherapy group and had numerically more cases of intracranial haemorrhage. The rate of all cause death was higher in dual therapy group than the monotherapy group these deaths were largely attributed to the increase in definite and probable vascular deaths [18]. The SPS3 trial clearly showed that the addition of clopidogrel to aspirin for long term therapy should be contraindicated in patients with lacunar infraction.

A recent metaanalysis of 7 trials includes dual antiplatelet therapy which was associated with a trend towards a reduction in recurrent stroke risk compared to aspirin monotherapy, but had no increase in the intracranial haemorrhage risk. Compared to clopidogrel monotherapy, dual therapy had a comparable risk reduction for recurrent stroke, but increased a higher risk of intracranial haemorrhage.

Dual antiplatelet therapy initiated early after ischemic stroke or TIA might further reduce recurrent stroke and major vascular events compared to antiplatelet monotherapy, with no significant increase in major bleeding events. In contrast, for the long therapy usually administered after a high-risk period, dual antiplatelet therapy is likely to increase the harm caused by major bleeding, including intracranial haemorrhage and its benefit of further preventing recurrent stroke as well as major ischemic events remains controversial. The risk of recurrent stroke is highest during the early period after ischemic stroke or TIA, but this risk decreases with time.

4. CONCLUSION

The studies have concluded that dual antiplatelet therapy more potently blocking platelet activation pathways have minimum risk of bleeding when given for short term use but have a higher risk of bleeding complications when given for a long-term use. Also, dual antiplatelet therapy which includes aspirin and clopidogrel is more effective than aspirin monotherapy or clopidogrel monotherapy but has a major side effect with long term therapy of intracranial haemorrhage. Thus, it is beneficial for the patient with TIA or ischemic stroke.

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