Original Research Paper

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Clinical Research

TRIPPLE ANTIPLATELET THERAPY IMPROVES CLINICAL OUTCOME IN PERCUTANEOUS CORONARY INTERVENTION (PCI) PATIENTS.

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ABSTRACT

Background : It has been demonstrated in previous large randomized studies that cilostazol based triple antiplatelet therapy (TAPT) in addition to aspirin and clopidogrel based dual antiplatelet therapy (DAPT) has improved the clinical outcomes in patients undergoing percutaneous coronary intervention (PCI).

Objective : The present study was conducted to compare the efficacy of triple versus dual antiplatelet therapy in patients undergoing PCI.

Material and methods : We enrolled 200 consecutive acute coronary syndrome patients undergoing drug eluting stents implantation. Half of the patients(n=100) received dual antiplatelet therapy (aspirin plus clopidogrel); rest half(n=100) received triple antiplatelet therapy (aspirin, clopidogrel plus cilostazol). The triple antiplatelet group received cilostazol at least for 1 month. The two group of patients were followed up at interval of 1, 3 and 6 months for any major adverse cardiac events. The triple antiplatelet group had more bleeding manifestations than dual group. At the end of six months follow up both groups had no statistically significant difference in terms of major adverse cardiac events. Target vessel revascularization was more in in the dual than the triple antiplatelet group.

Conclusions : Triple antiplatelet therapy seems to be superior to dual antiplatelet therapy in patients undergoing PCI with drug eluting stents.

KEYWORDS :

Introduction:-

Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a non-surgical method used to treat narrowed coronary arteries that supply the cardiac muscle with blood1. PCI has been clinically applied for almost 30 years and has become one of the main treatments for coronary heart disease (CHD) 2. PCI with coronary stent implantation has been demonstrated to consistently reduce the symptoms of coronary artery disease and decrease cardiac ischemia; however, PCI has not been shown to reduce mortality rates in large clinical trials 3. The implantable vascular stents used during PCI procedures appear to increase the risk of coronary artery intimal injury and platelet activation, and may thereby increase the risk of thrombosis4. This is significant, as the 1-year mortality rate of patients with myocardial infarction (MI) induced by thrombotic diseases is ~15.8% 5. Therefore, antiplatelet therapy has become the focus of basic interventional cardiology studies and has received increased clinical attention in the last decade6.

Dual antiplatelet therapy with aspirin and clopidogrel is currently the standard of care to prevent stent thrombosis after percutaneous coronary intervention with bare metal stent or drug eluting stent. 7 However there is significant interindividual variability in the extent of platelet inhibition achieved with these two antiplatelet agents.8 Cilostazol is a phosphodiesterase III inhibitor, exhibits its antiplatelet effects via inhibition of the conversion of cAMP to 5'- AMP causing a subsequent increase in cAMP in platelets and has been shown to augment platelet inhibition when added to aspirin and clopidogrel. In addition cilostazol inhibits neointimal hyperplasia and smooth muscle proliferation and has the potential to reduce the risk of restenosis after coronary stent implantation.Triple antiplatelet therapy with aspirin, clopidogrel and cilostazol has been tried in many trials in the era of drug eluting stents with mixed results.9 Because of its different pharmacokinetic action it may have an additive effect in patients undergoing PCI.

Registry data have further identified that TAPT reduces the rate of restenosis, incidence of clinical events and stent thrombosis, compared with DAPT10. However, controlled clinical studies that have examined the benefits of adding cilostazol to DAPT in patients with CHD undergoing PCI with coronary stent implantation have obtained conflicted or inconclusive results. Therefore, the present study is aimed to compare efficacy and differences in the clinical outcomes between DAPT and TAPT in patients with CHD undergoing PCI.

Aims And Objectives:-

To study the effect of triple antiplatelet therapy versus dual antiplatelet therapy in patients undergoing percutaneous coronary intervention by observing :

1. Total number of deaths after 6 months follow up . 2. Number of cardiac deaths and major adverse cardiac events (MACE) and MACCE (Major adverse cardiac and cerebrovascular events) at six months follow up. 3. Ischaemia driven target vessel revascularization at 6 months.

Methods:

All new consecutive acute coronary syndrome cases undergoing percutaneous coronary intervention in our institute with drug eluting stent implantation were enrolled as cases. Lesions that were hemodynamically significant i.e. more than 70% stenosis were planned for percutaneous coronary intervention using drug eluting stents.

Following PTCA patients were randomly assigned into two groups. Half of them (n=100) received dual antiplatet drugs (Aspirin and Clopidogrel) and the other half (n=100) received triple antiplatelet (Aspirin, Clopidogrel and additional Cilastazol therapy for 1 month. Various MACE and MACCE at 6 months were compared between these groups.

Inclusion criteria: Patients aged 18 years and above with acute coronary syndromes presented in cardiology department with history of chest pain and undergoing PCI.

Exclusion criteria: 1.Contraindication to aspirin, clopidogrel and cilostazol.2. Left main disease. 3. Graft versus host disease. 4. LVEF < 30%.

Statistical analysis:-

The following statistical methods were applied in the present study. Frequencies, Descriptive statistics, Cross tabs procedure(contingency coefficient test), Independent samples 't' test, Bivariate correlation, Logistic regression. Frequencies

The frequencies procedure provides statistics and graphical displays that are useful for describing many types of variables.

Descriptive :

The Descriptive procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which the variables are selected.

Crosstabs :

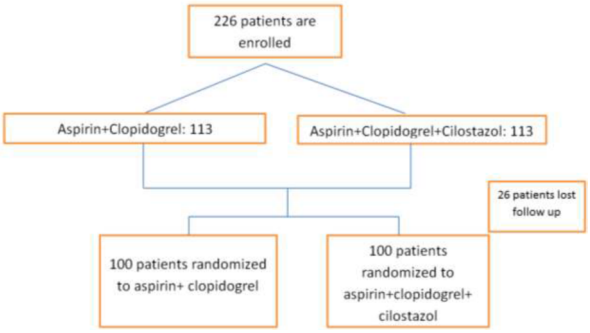
The procedure forms two way and multi way tables and provides a variety of tests and measures of association for two tables. The structure of the table whether categories are ordered determine what test or measure to use.

Independent-Samples T test :

It compares means for two groups of cases. Ideally, for this test, the subjects should be randomly assigned to two groups, so that any difference in response is due to the treatment (or lack of treatment) and not to other factors.

All the statistical analysis were done by SPSS 22 Inc. software.

Flow Chart



Result:-

The mean age of presentation in our study population was 63.81±8.71 years, with maximum number of patients between 61-70 years i.e. 87 (43.5%) number of patients, less number of patients in the age group of 41-50 years i.e. 20 (10%) as shown in table1. This is supported by K.P. Alexannder, et al.11

Table 1 -

Age in years	Frequency
41- 50	20(10%)
51-60	67(33.5%)
61-70	87(43.5%)
71-80	26(13%)

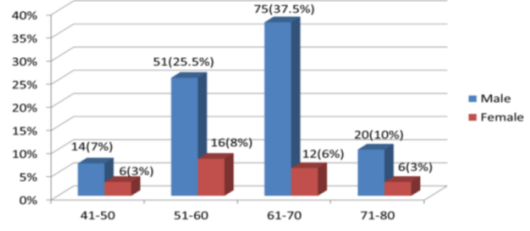
In our study male predominance was observed, i.e.male patients 80% (n=160) and female20% (n=40) which is same as **Annika Rosengren et al. 2004.**[12]

As shown in table 2 and figure 2 maximum numbers of male patients in our study are between age group of 61-70 years i.e. 75(37.5%) and minimum between 41-50 years i.e.14(7%). Maximum number of female patients are in the age group of 51-60 years i.e. 16 (8%). Our observation is supported by **Lozano R et al 2012.**[13]

Table 2 –

Age group	Male	Female
41-50 years	14(7%)	6 (3%)
51-60 years	51(25.55)	16(8%)
61-70 years	75(37.5%)	12(6%)
71-80 years	20(10)%	6(3%)

Figure 2:-



In our study as shown in table 3 maximum number of patients were having ST elevated myocardial infarction (STEMI) i.e. 134(67%), followed by Non ST segment elevated myocardial infarction (NSTEMI) 47(23.5%) and only 19(9.5%) patients have Unstable Angina (UA) which is in par with two Indian studies **Eagle K et al. and Prabhakaran D et al.**[14,15]

Table 3:-

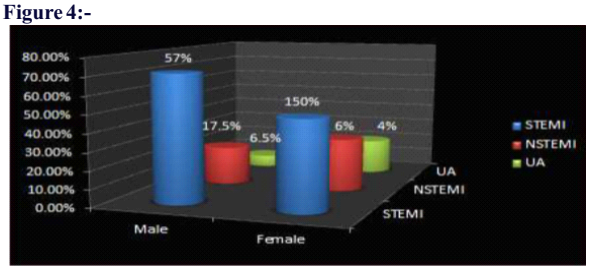
Disease	Frequency
STEMI	134(67%)
NSTEMI	47(23.5%)
Unstable Angina	19(9.5%)

In our study population as shown in table 4 and figure 4 male have more STEMI i.e. 114(71.25%) , followed by female 20(50%), where as female patients have more NSTEMI (30%) and Unstable Angina (20%) which is statistically very significant ($p < 0.003$) which is supported by **Prescott E et al and Aliah A et al 2017**.[16,17]

Table 4:-

Disease	Frequency	
	Male	Female
STEMI	114(57%)	20(10%)
NSTEMI	35(17.5%	12(6%)
Unstable Angina	11(5.5%)	8(4%)

Figure 4:-



In our study more number of patients i.e.163(81.5%) have undergone single vessel revascularisation than double vessel in 37(18.5%). Single stent was deployed in 115(57.5%), two stents in 76(38.5%) and three stents in 9(4.5%) patients of our study population.

Table 5 depicts the follow up symptoms at 1 , 3 and 6 months follow up. Most patients were asymptomatic at follow up visits same supported by **Fischman DL et al** [18], followed by chest pain and bleeding manifestations. Fatal myocardial infarction was observed in 4(2%) at 1 month , 3(1.5%) at 3 months, and 7(3.5%) at 6 months follow up. Randomized studies have revealed 6-month rates of angiographically demonstrated restenosis ranging from 32% to 42% after balloon angioplasty and from 16% to 32% after the implantation of a non–drug-eluting stent (bare metal stent, BMS) ; the 6-month rate of restenosis after the implantation of a drug-eluting stent is less than 10% contrary to our study **Serruys PW et al** .[19]

Table 5:-

Symptoms	1 month follow up	3 month follow up	6 month follow up
Chest pain	22(11%)	14(7%)	11(5.5%)
TIMI major Bleeding manifestation	14(7%)	17(8.5%)	17(8.5%)
Nonfatal MI	2(1%)	3(1.5%)	12(6%)
Fatal MI	4(2%)	3(1.5%)	7(3.5%)
Asymptomatic	158(79%)	163(81.5%)	153(76.5%)

DAPT group have more major adverse cardiac events (MACE) than TAPT group. But the analysis was statistically insignificant ($p < 0.087$). Our observation is supported by **Ahn Y et al**.[20]

In our study cohort correlation of dual versus triple antiplatelet therapy in terms of follow up symptoms like chest pain, fatal and nonfatal myocardial infarction, Chest pain and myocardial infarction was more in the dual antiplatelet (DAPT) group while TIMI major and minor bleeding manifestation was high in the triple antiplatelet (TAPT) group (shown in Table 6) which is statistically significant ($p< 0.008$) which is supported by **Young-Hoon et al.**[21]

Table 6:-

Anti platelet	Symptoms						
	Chest pain	TIMI Bleeding manifestations		Nonfatal MI	Fatal MI	None	Total
		Minor	Major				
Aspirin+Clopidogrel	7	2	0	3	2	86	100
Aspirin+Clopidogrel +Cilostazol	7	13	2	0	1	77	100
Total	14	15	2	3	3	163	200

The linear regression values of antiplatelet therapy in relation to target vessel revascularization showed that TAPT group had less TVR than DAPT which is statistically not significant which is similar to **Lee CH, et al.(DECREASE PCI-trial)** and contrary to the observation by **Sripal Bangalore et al**.[22]

More the number of stents deployed more is the MACE which was statistically highly significant (p <0.001). Our study is supported by **James E et al.**[23-25]

Discussion:-

In this prospective randomized study the efficacy of cilostazol as antiplatelet was compared with that of conventional dual antiplatelet drugs aspirin and clopidogrel in patients undergoing PCI. The results showed that in the triple antiplatelet therapy arm there was more bleeding risk. In terms of MACE triple antiplatelet therapy does not significantly score over DAPT. In follow up visits patients on DAPT had more history of chest pain, nonfatal. Stent thrombosis is a major concern for DES, cilostazol does not appear to provide benefit which shoud be interpreted cautiously in further large randomized studies. There was no statistically significant difference in the two groups in terms of TVR and TLR. The antiproliferative properties of cilostazol may have contributed to this beneficial effect. The limitations of this study was less number of patients enrolled and further follow up till one year could have added more information regarding efficacy.

Conclusion:-

Triple therapy with cilostazol has been shown to reduce MACEs by providing increased inhibition of platelet aggregation and reducing the rates of in-stent thrombosis compared to DAPT without increasing the risk of bleeding. Compared with DAPT, patients with a high risk of restenosis benefited from TAPT in reduced stent restenosis and revascularization after DES implantation, without increases in all-cause mortality and bleeding, but these outcomes were accompanied by a higher incidence of other adverse reactions and drug discontinuation. Further studies are needed to identify proper patient selection based on risk factors for the addition of cilostazol. Additionally, studies comparing cilostazol with newer antiplatelet therapies, such as prasugrel and ticagrelor, are needed.

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