"For one who has awakened in knowledge, there is no suffering."

Abstract
1: ABSTRACT

Cardiovascular disease (CVD) will be the leading cause of death and disability worldwide by 2020, mainly because it will increase in low and middle income countries. Ischemic Heart Disease (IHD) leading to the obstruction in coronary arteries (called as coronary artery disease/coronary heart disease) is the major cause of morbidity and mortality worldwide. The prevalence of CAD in India is about 10% and it is four times higher as compared to the U.S. Among the CAD, manifestations of acute coronary syndromes (ACS) (AMI and UA), chronic stable angina and heart failure constitute higher risk and treatment challenges in these patients. Inspite of the continuous development in therapeutic and interventional strategies within this franchise, burden of disease remains the challenge. There are very few data available which has evaluated the efficacy and safety of various drugs and medical devices for the treatment and management of these patients in India. We have evaluated comprehensively preventative therapy in hyperlipidemic patients as well as treatment of IHD patients presenting with ACS through medical management and specialized percutaneous coronary interventions (PCI) in four subsets of the study, pitavastatin vs. atorvastatin (preventive management); bivalirudin vs. heparin; abciximab vs. standard therapy and conventional stenting alone vs. conventional stenting followed by aspiration catheter. The protocols were approved by the Institutional Review Board (IRB) and patient's consent was taken before enrollment into study.

An elevated level of low density lipoprotein cholesterol (LDL-C) is the most important risk factor for IHD/CAD. Development of the HMG-CoA reductase inhibitors is a rate limiting key enzyme of cholesterol synthesis pathway, has revolutionized the cholesterol lowering therapy. Effective primary and secondary measure have been established in several statin trials to prevent future events of CAD by lowering LDL cholesterol levels. To date, atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin and cerivastatin have been used. Pitavastatin is a new highly effective statin in reducing LDL as compare to pravastatin, simvastatin and atorvastatin. We evaluated the safety and efficacy of pitavastatin in hyperlipidemic patients focusing primarily on percent change in LDL-C and apolipoprotein B (Apo B); target attainment of Total cholesterol (TC),
high density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Safety was assessed by measuring the elevations of hematology and biochemistry parameters such as hepatic enzymes, high sensitivity C-Reactive Protein (hsCRP) and creatinine phosphokinase (CK) levels. Clinical assessment was also done during the treatment period.

The evaluation of statins was carried out in 50 prospective hyperlipidemic patients meeting baseline eligibility criteria. The patients were randomized in two groups; Group I [pitavastatin (2 mg/day), test drug, n=25] and Group II [atorvastatin (10 mg/day, n=25), standard drug]. Patient’s demographics, risk factors, hemodynamic, medical and cardiac history, hematology, biochemistry, biomarkers, and lipoproteins parameters were recorded. Lipoprotein parameters which included serum TC, TG, HDL-C, LDL-C and Apo B were measured. Percentage change in LDL-C from baseline at week 24 and week 52 was the primary endpoint of the study. Mean change in LDL-C, TC, HDL-C, TG, and Apo B levels from baseline were measured on week 12, 24, 36, 48 and 52 as secondary endpoint of the study. Clinical examinations and laboratory investigations like hepatic enzyme levels, CK and hsCRP levels were checked during treatment period on week 24 and week 52. Urine myoglobin levels were recorded throughout the study (baseline, week 12, 24, 36, 48 and 52) as a safety parameter.

Use of pitavastatin showed significant reduction of LDL-C on week 24 (28% vs. 23%, p<0.001) and week 52 (45% vs. 33%, p<0.001) from baseline. There was significant reduction in Apo B levels on week 24 (22% vs. 15%, p<0.001) and week 52 (36% vs. 31%, p<0.05) from baseline in Group I. Pitavastatin treated patients showed significant improvement in the TC, TG and HDL-C levels on week 52 from baseline. No significant elevations in hepatic enzyme, CK, hsCRP and urine myoglobin levels were observed in both the groups from baseline till the end of the treatment period. No clinical adverse events were reported during 52 weeks of treatment period in both the groups. Thus, long term use of pitavastatin was found to be effective and safe at minimal dose for reduction in LDL-C and Apo B levels and attainment of NCEP ATP III target goal.

Both PCI and ACS disrupt the integrity of the arterial wall, these intimal defects and subsequent thrombosis leads to myocardial infarction (MI). Antithrombotic agents have been the mainstay of both medical and interventional approaches to patient
management. The central role of thrombin in the initiation and propagation of intravascular thrombus provides a strong rationale for direct thrombin inhibitors in ACS. Direct thrombin inhibitors are likely to be more effective than indirect thrombin inhibitors such as UFH/LMWH, whereas direct thrombin inhibitors block both circulating and clot-bound thrombin. Bivalirudin is a direct thrombin inhibitor that has several advantages over heparin. In the several studies, bivalirudin monotherapy resulted in significant reduction in rates of major and minor bleeding and ischemic events and deaths in stable or unstable angina (UA) that were undergoing PCI as compared to UFH and GP IIb/IIIa inhibitor. Hence, we evaluated the efficacy and safety of bivalirudin as part of an early invasive strategy with optimal antiplatelet therapy in ischemic patients presenting with ACS, focusing primarily on optimal outcome in activated clotting time (ACT) by annihilating thrombus load, assessing coronary epicardial (TIMI III) and myocardial perfusion (TMP 3), occurrence of major bleeding and MACE [death, recurrent myocardial infarction (ReMI), target vessel revascularization (TVR), emergent PCI or coronary artery bypass graft (CABG) and sub-acute thrombosis (SAT)].

The evaluation of bivalirudin and heparin was carried out in 203 prospective IHD patients presenting with ACS meeting the eligibility criteria and undergoing PCI. The patients were randomized in two groups; Group I (bivalirudin, test drug, n=94) and Group II (heparin, standard drug, n=109). The baseline characteristics like demographics, previous cardiac history, and the angiographic parameters were assessed. ACT (10 min; end of the procedure) and sheath removal time after PCI was determined. Bleeding events were recorded during and till hospital discharge/ day 7 whichever was earlier. The in-lab complications & peri-procedural events such as no-reflow/slow flow, distal embolization, thrombus formation, side branch closure were recorded; provisional use of GP IIb/IIIa inhibitors and composite end point which includes death, MI, revascularization, SAT was also recorded during the hospital stay. The final TIMI and TMP grade after PCI were assessed. The patients were followed at day 7, day 30 & at 1 year for any clinical events.

Use of bivalirudin showed significantly greater achievement of ACT after the 10 min of bolus administration (311.98±76 sec vs. 257.0±16 sec, p<0.001) and at the end of the procedure (298.1 ± 90.8 sec vs. 224 ± 153 sec, p<0.001). The percentage of patients required the additional bolus to achieve ACT was significantly lesser (2.5% vs. 12%,
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$p<0.05$) in bivalirudin group as compared to heparin group. The time (hr) to remove sheath after PCI was significantly reduced (1.75±1.0 vs. 3.5±0.5, $p<0.001$) in bivalirudin as compared to heparin. Patients treated with bivalirudin showed significant ($p<0.001$) achievement in the epicardial flow (TIMI III flow) and myocardial blush (TMP 3) grade. Percentage of patients with TIMI III flow (95% vs. 78%, $p<0.001$) and mean TMP 3 grade (90% vs. 72%, $p<0.05$) was significantly higher in group I. In patients with clinically significant thrombus load, achievement of mean TIMI III flow (2.18±0.3 vs. 2.45±0.2, $p<0.001$) and TMP 3 grade (2.67±0.4 vs. 2.1±0.2, $p<0.001$) was significantly higher and no reflow at the end of PCI was significantly lesser (5% vs. 16%, $p<0.05$) in Group I as compared to Group II. The incidence of no-reflow/slow flow, distal embolization, thrombus formation, side branch closure was significantly reduced in bivalirudin treated patients, thus reducing the usage of GP IIb/IIIa inhibitors (6% vs. 22%, $p<0.05$) and intracoronary vasodilators (10% vs. 29.4%, $p<0.001$). No incidence of major bleeding was recorded in bivalirudin treated patients while three events of major bleeding were reported in heparin treated patients. The mean duration of hospital stay was significantly less in bivalirudin treated patients (2.3 ± 1.6 days vs. 2.9 ± 1.9, $p<0.05$).

Improvement in clinical outcome was observed in bivalirudin treated (one non cardiac death, ~1.0%) as compared to heparin (three cardiac deaths, 2.75% and one in-stent restenosis, 0.91%) on day 7. On day 30, one non cardiac death (0.91%) in bivalirudin treated patients while and one individual event of cardiac death (1.06%), urgent revascularization (1.06%) and sub-acute thrombosis (1.06%) occurred in heparin treated patients. No clinical events occurred in both the groups at one year. Thus, the use of bivalirudin as adjunct to PCI in IHD patients presenting with ACS was effective and safe. It was associated with no incidence of major bleeding and less ischemic events at day 7, day 30 and on one year.

Antiplatelet drugs played a major role for the management of ACS. Aspirin and clopidogrel are recommended as first-line treatment in the guidelines. In high-risk patients (with recurrent ischemia, ST-segment depression, elevated troponins, and diabetics (ESC guidelines) and moderate-to-high-risk patients (TIMI risk score in the ACC/AHA guidelines), GP IIb/IIIa receptor inhibitor are recommended to the baseline
treatment. In a meta-analysis of trials involving ACS patients, addition of GP IIb/IIIa inhibitor along with the primarily medically managed resulted in reduced rates of death and MI especially in patients undergoing PCI during index hospitalization. In several studies it has been reported that the use of abciximab has been shown to reduce ischemic cardiac complications in high risk patients undergoing PCI. Hence, we evaluated the safety and efficacy of abciximab at the top of standard therapy and compared against the standard therapy alone in moderate to high risk ACS patients undergoing PCI, focusing primarily on clinical outcomes like incidences of cardiac death, MI, urgent revascularization (PCI or CABG), sub acute vessel occlusion or SAT and safety parameters included occurrence of bleeding (major or minor), thrombocytopenia, change in Hemoglobin (Hb)/ Hematocrit (Hct) and any other adverse events (AEs) after infusion of abciximab till day 30 follow-up.

The evaluation of abciximab (triple antiplatelet therapy i.e. aspirin, clopidogrel and abciximab) and standard therapy alone (aspirin, clopidogrel) was carried out in 120 prospective moderate to high risk ischemic patients presenting with ACS meeting the eligibility criteria and undergoing PCI. The patients were randomized into two groups; Group I (abciximab + standard therapy, test group, n=60) and Group II (standard therapy, standard group, n=60). The patient’s demographics, medical and cardiac history, cardiac indications, risk factors, hemodynamic, physical examination, and pathologic findings were assessed. The ischemic improvement was assessed by electrocardiography (ECG) at pre and post procedure (24 hr), on day 7 and day 30. The blood platelet counts and Hct level was assessed to keep check on incidence of thrombocytopenia. Clinical outcome was assessed by recording MACE during hospital stay, day 7 and day 30 day after infusion of abciximab at top of the standard therapy.

Patients treated with abciximab along the standard therapy showed significant improvement in ischemic outcome assessed by ECG at 24 hr (65% vs. 38%, p<0.001), on day 7 (73% vs. 50%, p<0.05) and on day 30 (85% vs. 57%, p<0.001). There was no significant difference in CK-MB, Hb/Hct, and platelets counts between both the groups at 12 hour, 24 hour, day 7 and day 30. Incidence of side branch closure was observed in one patient in Group II during PCI procedure. Occurrence of one minor bleeding (1.67%, at 4 hour), two minor gum bleeding (3.33%, at 6 hour) one event each of hematoma (1.67%,
at 6 hour) and mild thrombocytopenia (<1,00,000) (1.67%, at 12 hour) was reported after the infusion of abciximab while one event each of hematuria (1.67%, at 24 hour) and thrombocytopenia (1.67%, on day 7) occurred in patient treated with standard therapy alone. On day 7, in Group I no cardiac event was observed while one cardiac death was reported in Group II. No adverse clinical events occurred in both the groups on day 30. Thus, use of abciximab at the top of standard therapy has effectively reduced the ischemic cardiac complication, improved the quality of life without increasing the risk of major bleeding in moderate to high risk IHD patients presenting with ACS and undergoing PCI.

Distal embolization of particulate matter formed of plaque debris and thrombus in coronary arteries complicates PCI which results in no-reflow/slow-flow, diminished blood flow to the distal vascular bed, failure to achieve adequate reperfusion resulting from necrosis of myocytes and microvascular network, periprocedural end-organ ischemia, infarction and restenosis. In an effort to reduce complications such as distal embolization and no-reflow, aspiration catheter (EXPORT catheter) which is component of Percusurge Guard Wire™ system has been used. Clinical data on the use of aspiration catheter in acute MI (AMI) patients undergoing PCI is less. Clinical studies have shown that stenting in combination with the aspiration catheter in AMI patients is safe and effective in terms of retrieving debris, improvement in post-procedure epicardial flow and myocardial blush. We evaluated the effect of aspiration catheter followed by stenting in IHD patients presenting with AMI with the aim to find out whether the use of primary aspiration could reduce the complication rate of PCI, allowing removal of embolic debris by focusing primarily on clinical events (MACE: death, target lesion/vessel revascularization, myocardial infarction and sub acute thrombosis), procedural, device and angiographic success; restoration of epicardial and myocardial flow; and improvement in ST resolution was assessed by ECG.

The evaluation of aspiration catheter was carried out in 50 prospective ischemic patients presenting with AMI and undergoing PCI within 24 hour of onset of symptoms. The patients were randomized into two groups; Group I [conventional stenting alone (PCI without use of aspiration catheter), control group, n=25] and Group II (PCI with primary
aspiration using aspiration catheter followed by conventional stenting, test group, n=25). Along with conventional demographic and angiographic characteristics, parameters including TIMI flow and TMP grade pre-procedure, after aspiration and post-procedure; resolution of ST segment elevation, successful aspiration of thrombus by the catheter without any complications, usage of the GP IIb/IIIa inhibitor and intracoronary vasodilators to combat slow flow and no-reflow, and clinical outcomes (during hospital stay, day 7, day 30 and on one year) were evaluated in both the groups. The total procedural time was also recorded.

Use of aspiration catheter followed by conventional stenting has successfully removed the thrombus burden without any complication (100% device success) leading to the significant improvement in % of patients to achieve final restoration of epicardial flow (TIMI) (100% vs. 72%, \( p<0.001 \)) and myocardial blush (TMP) (92% vs. 60%, \( p<0.001 \)) at the end of the procedure. The use of drug eluting stent (DES) after primary aspiration was significantly less (48% vs. 24%, \( p<0.001 \)) in Group II. The incidence of slow flow/no-reflow, distal embolization and side branch closure was significantly lesser due to aspiration which reduces the usage of GP IIb/IIIa inhibitors (25% vs. 75%, \( p<0.001 \)) and intracoronary vasodilators (16% vs. 44%, \( p<0.001 \)). Achievement of ST segment resolution in patients was significantly higher (88% vs. 65%, \( p<0.001 \)) due to aspiration as compared to conventional stenting alone at 24 hour of the PCI. Requirement of pre-dilatation (24% vs. 56%, \( p<0.05 \)) and post-dilatation (4% vs. 20%, \( p<0.05 \)) was significantly lesser in patient underwent primary aspiration in addition to the conventional stenting. The duration of total procedural time was significantly reduced following primary aspiration (19.4±6.38 vs. 26.96±10.37, \( p<0.05 \)). Incidence of three cardiac deaths and one urgent revascularization in Group I, while one cardiac, one non cardiac and one SAT in Group II was recorded on day 7/hospital discharge. One cardiac death was reported in control group on day 30. No adverse clinical event was reported at one year follow up. The primary aspiration has improved the rate of ST segment resolution, reduced the event of distal embolization, decreased the procedural time with better and faster optimal restoration of epicardial flow and myocardial perfusion, and lesser long term cardiac events in IHD patients presenting with AMI and undergoing PCI.