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Case Report

Retroperitoneal Bleed with Ticagrelor Administration Following Fibrinolytic Therapy in Acute ST-Elevation Myocardial Infarction

Venkatesh Tekur Krishnamurthy

Department of Cardiology, Apollo hospitals 154/11, Opp IIM-B, Bannerghatta Road Bangalore 560076 India.

ABSTRACT

ST-elevation myocardial infarction, in anticipation of primary percutaneous coronary intervention, clopidogrel, prasugrel or ticagrelor are given with Aspirin on presentation. The Authors report a case of acute ST elevation anterior wall myocardial infarction administered ticagrelor with Asprin with intent to treat by primary percutaneous coronary intervention, but patient subsequently opted for intravenous fibrinolytic therapy instead of primary percutaneous coronary intervention. Although fibrinolytic therapy was successful in achieving reperfusion, patient developed significant retroperitoneal bleed requiring multiple blood transfusions. Only clopidogrel is recommended in the setting of fibrinolytic therapy in the guidelines and no data are presently available with ticagrelor.

Key words: ST elevation myocardial infarction, Ticagrelor, Fibrinolysis, Primary percutaneous coronary intervention (PCI).

Correspondence

Venkatesh Tekur Krishnamurthy,

Department of Cardiology, Apollo hospitals 154/11, Opp IIM-B, Bannerghatta Road Bangalore560076 India.
Phone no: +91 9844075579

Emai: venkateshtekur@yahoo.com

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INTRODUCTION

In ST-elevation myocardial infarction, complete occlusion of culprit coronary artery occurs in majority of patients. It is important that the artery is opened as soon as possible to restore blood to the jeopardized myocardium and direct coronary intervention is considered the appropriate care. In a setting of primary percutaneous coronary intervention (PCI), dual antiplatelet therapy with prasugrel or ticagrelor or clopidogrel,are recommended in addition to Aspirin at presentation. Available recommendations indicate administration of clopidogrel only after fibrinolytic therapy, due to concern that ticagrelor is more potent and combining such a potent antiplatelet agent with fibrinolytic therapy might increase the risk of bleeding. An environment of increased tendency to bleed is created when fibrinolytic therapy has to be carried out instead of primary PCI. We report significant retroperitoneal bleed requiring multiple blood transfusions when ticagrelor is followed by fibrionolytic therapy in a setting of acute ST elevation myocardial infarction.

CASE REPORT

A 50-year male presented with severe central, retrosternal chest pain of 30 minutes duration. ECG showed acute anterior ST-elevation myocardial infarction. He received Aspirin 325 mg with Ticagrelor 180 mg with a plan for primary PCI. He also received Tab. Atorvastatin 80 mg. After 5 minutes after administering dual antiplatelet therapy, patient changed his preference, refused primary PCI and instead opted for fibrinolytic therapy. After explaining the risks and benefits of fibrinolytic therapy, he was administered Reteplase 10 units Intravenous bolus (over 2 minutes), followed by second dose after 30 minutes-(for total cumulative dose of 20 units). A good resolution of ST-elevation on ECG indicated benefit with reperfusion. After 2 hours patient developed hypotension (90/70mm Hg) and he complained of severe backache, abdominal and bilateral flank pain. There was a significant drop of hemoglobin by more than 5g/dL. Prothrombin time increased from 11.5 seconds to 22.0 seconds.

Partial thromboplastin time was markedly prolonged - greater than 100 seconds. Echocardiogram showed good LV systolic function. Blood transfusion was started and he was investigated immediately by CT scan abdomen. CT abdomen showed diffuse retroperitoneal hematoma involving lateroconal fascia bilaterally, right more than left, right posterior perirenal fascia, perivesical, prevesical space and presacral regions. The fluid layering was hyperdense at places suggestive of hematoma.The picture was one of spreading linear tracks rather than focal collections. (Figure 1). Patient was managed conservatively and after multiple blood transfusions, he improved and was discharged from the hospital after 3 days.

DISCUSSION

Following an Acute coronary syndrome, it is shown that dual antiplatelet therapy is effective in decreasing cardiovascular events both short term and at 12 months. The newest oral antiplatelet agent that is indicated for the treatment of patients with ST-elevation myocardial infarction, Non-ST-elevation myocardial infarction, as well as unstable angina is Ticagrelor. This is regardless of whether the patient is managed medically or with catheter based coronary intervention or by surgical revascularization. In ST-elevation myocardial infarction patients, time is of essence, and there is a need to administer early therapy. Early therapy may be as intravenous fibrinolytic therapy or as percutaneous coronary intervention with initial administration of dual antiplatelet agents. The role of dual antiplatelet drugs are mainly to prevent stent thrombosis soon after percutaneous coronary intervention. Hence antiplatelet agents with faster onset of action are preferred in this setting. Newer antiplatelet drug which have potent antiplatelet activity and fast onset of action like Ticagrelor are increasingly used in the setting of ST-elevation acute myocardial infarction. If a centre does not have a facility for immediate percutaneous intervention, then intravenous fibrinolytic therapy is administered as a life saving measure. With fibrinolytic therapy, Ticagrelor should not be utilized. It is not listed as an alternative in any of the the guidelines. The reason is the perception of increased risk of bleeding occurring in a patient when potent, newer and powerful antiplatelet agents like Ticagrelor or Prasugrel are combined with intravenous fibrinolytic agents. The guidelines are very specific in recommending only clopidogrel with fibrinolytic therapy.[1] The beneficial effects of aspirin and clopidogrel with fibrinolytic therapy are well established.[2,3,4,5] Patients with ST-elevation myocardial infarction should receive clopidogrel at the time of administration of a fibrinolytic agent as a routine part of a pharmacological reperfusion strategy. Clopidogrel should be continued in uninter-

rupted fashion through and after percutaneous coronary intervention; and be continued for atleast one year. The recommendation that clopidogrel be continued for up to 1 year is extrapolated from the experience with dual antiplatelet therapy in patients with non–ST-elevation acute coronary syndrome.[6] Aspirin and Clopidogrel should be given before or with the fibrinolytic agent. There are no studies available showing the effects of combining fibrinolytic therapy with the newer antiplatelet agents like Ticagrelor or Prasugrel to the best of the Authors knowledge. The coadministration of other antiplatelet agents with fibrinolytic therapy has not been prospectively studied. The risk of bleeding when antiplatelet agents other than clopidogrel are combined with fibrinolytic therapy are not known. In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis In Myocardial Infarction 28) trial,[7] percutaneous coronary intervention was performed *2 to 8 days after fibrinolysis,* in about half of the enrolled patients, and open-label clopidogrel (300 - mg loading dose, 75 - mg maintenance dose) was administered after diagnostic angiography in patients undergoing infarct artery stenting. Treatment with clopidogrel significantly reduced the incidence of cardiovascular death, myocardial infarction, or stroke (major secondary composite endpoint) after percutaneous coronary intervention. In addition, there was no significant increase in the rates of Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding with clopidogrel treatment. However, Prasugrel can be used in the setting of *delayed* – which is, more than 24 to 48 hours after fibrinolytic therapy. In a trial, Prasugrel was administered after 24 hours after fibrinolytic therapy. A subset of patients with ST elevation myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38 trial) received fibrinolytic therapy >24 hours (for fibrin-specific agents) or >48 hours (for non–fibrin-specific agents) before percutaneous coronary intervention. In this subset, the use of prasugrel compared to clopidogrel was associated with a significantly lower rate of the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (HR: 0.65; 95% CI: 0.54 to 0.87; p=0.0017), and a similar rate of TIMI major bleeding unrelated to CABG.[8] Accordingly, Prasugrel (60 - mg loading dose) may be used as an alternative to clopidogrel in patients with ST elevation myocardial infarction who undergo delayed percutaneous coronary intervention after administration of a fibrinolytic agent. When using fibrinolytic therapy as the sole strategy, the only drug that's been studied is clopidogrel in conjunction with aspirin and heparin. In individuals who go on to percutaneous coronary intervention after fibrinolytic therapy, either for bailout or for recurrent symptoms, both clopidogrel and prasugrel have been studied. In hospitals where fibrinolytic therapy may be the primary reperfusion strategy, as per guidelines, clopidogrel alone is the antiplatelet of choice in addition to Aspirin. Use of one of the more potent drugs like prasugrel or ticagrelor would increase the risk of major bleeding. The reasons why guidelines have excluded Ticagrelor and Prasugrel are two-fold. One is

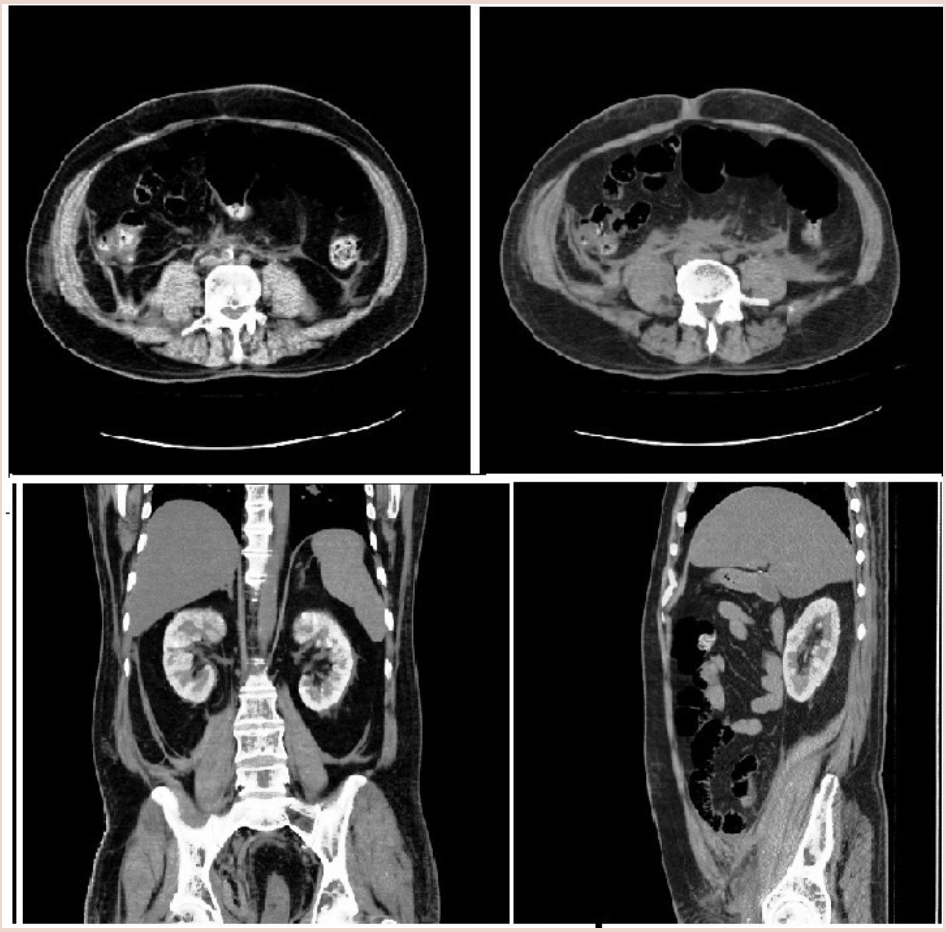

Figure 1: CT abdomen showing diffuse hyperdense fluid layering as spreading linear tracks rather than focal collections involving lateroconal fascia bilaterally, right more than left, right posterior perirenal fascia, perivesical, prevesical space and presacral regions suggestive of retroperitoneal hematoma.

that it was an exclusion criterion in the Platelet Inhibition and Patient Outcomes (PLATO) trial (no fibrinolytic therapy within 24 hours of randomization), which was probably due to concern that ticagrelor was more potent and that combining such a potent antiplatelet agent with fibrinolytic therapy might increase the risk of bleeding, and second, it was associated with more major bleeding, at least in those who were not managed with bypass.[9] Although presently evidence exists for exclusion of Ticagrelor or Prasugrel when fibrinolytic therapy is planned, no data exists for the occurrence of major bleeding when ticagrelor is initially administered with an intention to percutaneous coronary intervention , but, patient prefers receiving fibrinolytic therapy instead, to the best of Authors knowledge. "Ticagrelor for percutaneous coronary intervention Post Thrombolysis (Set Fast) Trial", is proposed to study the safety and efficacy of Ticagrelor in patients undergoing percutaneous coronary intervention after fibrinolytic therapy for ST elevation myocardial infarction. Here Ticagrelor will be administered as early as 4 hours after fibrinolysis. The trial has commenced on May 2014 with estimated study completion in December 2016. The trial involves recruiting patients above 18 years, to compare the administration of Ticagrelor in one arm to Clopidogrel in another, and will be conducted in patients who undergo percutaneous coronary intervention between 4-24 hours after administration of fibrinolytic therapy for ST elevation myocardial infarction. In the patient reported here, the Authors highlight the occurrence of major retroperitoneal bleeding when Ticagrelor was combined as a second antiplatelet agent to Aspirin prior to immediate but unintended fibrinolysis.

CONCLUSION

Major retroperitoneal bleeding can occur when Ticagrelor is administered after fibrinolytic therapy in Acute myocardial infarction.

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Nil

CONFLICT OF INTEREST

Nil

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