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Case Report *Medical research*

Severe upper gastrointestinal bleeding with gastric ulcer and anaemia secondary to prolonged use of aspirin and clopidogrel – A case report

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ABSTRACT

A combination therapy of aspirin with clopidogrel is useful in the prevention of various disorders of cardiovascular system, secondary prophylaxis thrombosis of systemic to pulmonary artery shunts, acute ST-segment elevation myocardial infarction and percutaneous coronary intervention. Traditionally, aspirin has been used for such conditions alone. Clopidogrel is as an alternative choice for aspirin. While the combination therapy shows a better outcome, but also has been associated with risks. Upper gastrointestinal bleeding (UGIB) is one such known adverse effect caused by fibrinolytic therapy, but it normally subsides itself without any treatment and is rarely serious, where the patient requires intensive care and monitoring during hospitalization. And, ulcers are the most common cause of hospitalization for UGIB. Anaemia can be seen in UGIB patients due to ulcers induced by the aspirin plus clopidogrel therapy. Here, we report a serious case of UGIB, gastric ulcer and anaemia in a 66-year-old male patient with structural valve deterioration and stent and upon long term use of combination therapy of aspirin and clopidogrel.

Key words: Aspirin, Clopidogrel, Serious Upper-Gastrointestinal Bleeding, Anaemia, Gastric ulcer

INTRODUCTION

Aspirin and clopidogrel alone or in combination (dual antiplatelet therapy) is used to prevent disorders of cardiovascular system, secondary prophylaxis for thrombosis of systemic to pulmonary artery shunts, **a**cute ST segment elevation myocardial infarction, percutaneous coronary intervention. [1] The combination therapy shows a better outcome, but has associated with risks. Upper gastrointestinal bleeding (UGIB) is a known adverse effect caused due to prolonged use of antiplatelet therapy but sudden occurrence of serious conditions requiring intensive medical care and hospitalization due to the same is rare. [2]

The serious adverse events reported for aspirin use includes gastrointestinal ulcer and UGIB and, the serious adverse events reported for clopidogrel use system-wise are *cardiovascular:* coronary artery stent thrombosis, *gastrointestinal*: colitis, gastrointestinal hemorrhage (2%), *hematologic*: agranulocytosis (upto 1%), aplastic anaemia (up to 1%), bleeding, major (0.8% to 3.7%), pancytopenia (severe) and thrombotic thrombocytopenic purpura. And, the adverse events reported for combination of aspirin plus clopidogrel

use includes gastric ulcer and duodenal ulcer, 0.1% to less than 1% gastrointestinal hemorrhage (1% to 10%), erosive gastritis (less than 0.01%). [2, 3]

Ulcers are the most common cause of hospitalization for UGIB, and the vast majority of clinical trials of therapy for non-variceal UGIB focus on ulcer disease[4]. Anaemia also can occur with increased severity of UGIB caused due to severe ulceration in the upper gastrointestinal tract. [3, 4]

UGIB in general has four times increased rates when compared to that of lower gastrointestinal bleeding. The annual incidence of UGIB ranges from 48 to 160 cases per 1 hundred thousand individuals. [5] UGIB annually has a hospitalization rate of 165 per 1 hundred thousand adults at an estimated cost of 2.5 billion annually. There are more number of reported cases of hospitalization due to UGIB than for only chronic heart failure or deep vein thrombosis. [6]

This case was medically important because of the severity of the UGIB, anaemia and pain due to ulceration and bleeding in the abdomen, which led to need for medical care and hospitalization.

CASE REPORT

A 66-year-old male patient came to hospital with the complaints of generalized weakness, with stool discoloration (malena), dyspnoea on exertion, increased urinary frequency and thirst since one week. He is a known case of structural valve deterioration with proximal right coronary artery stent since one year. There is no significant family history. The patient's history shows that he was on aspirin (75mg) and clopidogrel (75mg) since one year. He is also an occasional consumer of alcoholic beverages but didn't consume alcohol since four months.

Considering the seriousness, the patient was admitted to the hospital and upon examination, his vitals were found to be: BP= 140/85 mm of Hg, Pulse=83 bpm, respiratory rate= 12/min, SpO_2= 95% on room air and RBS= 165 mg/dl. Cardiovascular system: S1S2+; Respiratory system: normal vesicular breath sounds heard; Gastrointestinal system: abdomen-soft, non-tender; CNS: no abnormality detected. Laboratory investigation indicated of anaemia with decreased haemoglobin level (8.2 g/dL). Ultrasonography was done and it shows 'mildly altered renal parenchymal echogenicity bilaterally' and gastroscopy report confirmed of 'antral ulcer'. Colonoscopy was also done and no abnormality detected. Considering his history of structural valve deterioration and proximal right coronary artery stent, cardiologist's opinion was taken which was normal with no new findings.

The case was diagnosed as 'Severe UGIB, Gastric Ulcer and Anaemia Secondary to Prolonged Use of Aspirin and Clopidogrel'. Patient was started on intravenous fluids and blood transfusion was started with antibiotic (intravenous ceftriaxone, 1g, 1-0-1) considering the possibility of bacterial cause for bleeding and other supportive medications were intravenous pantoprazole, 40 mg, 1-0-0 and intravenous ondansetron, 4 mg, 1-1-1. The patient's condition significantly improved upon medical care and he was discharged after one week of hospitalization. Discharge medications included oral clopidogrel, 75 mg 1-0-0, (to continue) with oral domperidone, 10 mg 1-0-1, for 10 days (before food) and oral rabeprazole, 20mg 1-0-1, for one month. Oral aspirin was withheld due to its lesser safety profile when compared to clopidogrel. Patient was found to be recovered after two weeks on cessation of the suspected drug.

DISCUSSION

Oral aspirin has higher risk of UGIB over oral clopidogrel usage as a daily dose. The risk increases by a factor of two to three times when aspirin is used by inhibiting gastric cyclooxygenase and causing gastric ulceration. It blocks platelet aggregation and prevents thrombosis through cyclooxygenase enzyme inhibition which also induces gastric ulceration through same mechanism of action. [7] While clopidogrel has its effect by blocking the platelet aggregation of adenosine diphosphate which prevents the activation of the glycoprotein IIb/IIIa complex [8] with lesser incidence of causing UGIB. [8, 9] Hence, clopidogrel is preferred over aspirin for safety profile of clopidogrel.

Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Event (CAPRIE) steering committee conducted a study on 430 patients in the period between 1985 to 1989 for aspirin use and complications. Complications were gastrointestinal hemorrhage that required medication discontinuation, hospitalization, or transfusion;

intracerebral hemorrhage; subarachnoid hemorrhage; hemorrhagic transformation of ischemic stroke that resulted in new signs or symptoms; and hemorrhage that resulted in hospitalization, transfusion, intubation, surgical intervention, or death. It was concluded that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death. The overall safety profile of clopidogrel was found at least as good as that of medium-dose aspirin. [9] This study is similar to what we observed in our patient's case.

Vikas Kohli *et al* reported a clinical brief for a case of 3 year old male child with massive UGIB, shock, anaemia (haemoglobin 6.8 g%) and was confirmed to be due to long term use of combination therapy of aspirin and clopidogrel. He concluded that the combination of aspirin and clopidogrel can possibly result in massive near fatal bleeds as in the case he had reported and single drug use maybe preferred. [10] This case report presented similar UGIB with prolonged use of dual antiplatelet therapy as in our patient's case and also similar use of a single agent, preferably clopidogrel was advised considering the safety profile of clopidogrel.

Chan *et al* published an article that suggested that patients receiving clopidogrel had an astonishing increase in the rate of recurrent UGIB from ulcers, as compared with those patients in the group taking aspirin with esomeprazole (8.6 percent *vs.* 0.7 percent, P=0.001). It explained that for the increased bleeding by this antiplatelet agent, impairment of healing induced by clopidogrel may be the primary mechanism. Apart from the aspirin and clopidogrel issue, possibility of previous esophageal surgery to be a cause of the UGIB was also evaluated in this report. [11] The study was contrary to the current literature where we concluded aspirin to be the major reason for the bleeding and continued with clopidogrel as it was found comparatively safer.

Edward S. Huang *et al* published results for clinical research study for prospective cohort, long-term, regular aspirin use which was associated with increased risk of major gastrointestinal bleeding. They also suggested that altering duration of aspirin and controlling for other known or suspected risk factors did not alter these findings. The authors also suggested the potential implications for long-term aspirin use in the prevention of chronic disease and that the risk of gastrointestinal bleeding seems more strongly related to dose than duration of aspirin use. These results suggested that the adverse effects of aspirin therapy can be minimized by using the lowest effective dose among both short- and long-term users. [12] This was similar to our patient's case, where we attributed the cause of UGIB to be aspirin related. But, in this case, we did not decrease the aspirin dose to lowest therapeutic dose possible but instead stopped the aspirin completely because of the severity of our patient's case.

Our treatment approach used in this patient's case was also consistent with the American College of Cardiology–American Heart Association practice guidelines, which recommend the use of clopidogrel as an alternative antiplatelet agent for patients who have major gastrointestinal intolerance of aspirin. [13] The gastrointestinal intolerance of aspirin was attributed the cause for the ulcer to develop in this case which resulted in severe UGIB and caused anaemia as the patient was unable to eat properly due to ulcer in upper gastrointestinal tract and the severe bleeding from the ulcerated gastrointestinal tract as well.

CONCLUSIONS

The use of aspirin and clopidogrel (dual antiplatelet therapy) for long term prophylaxis should be based upon the clinician's judgement of potential risk and benefit of the therapy. And caution should be taken with regular monitoring for the symptoms of UGIB and ulcer, which increases the disease burden for the patient apart from the disease condition for which aspirin plus clopidogrel is being given to the patient. Also, clopidogrel use alone can be considered a better option when there is any evidence of UGIB or ulcer due to aspirin use.

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