Original Article

Safety of Clopidogrel in Ischemic Heart Disease Patients having Cirrhosis with Upper GI Bleed

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ABSTRACT

Objective: To evaluate the safety of clopidogrel in ischemic heart disease patients simultaneously suffering from cirrhosis with upper G bleed.

Study Design: A randomized controlled trial study.

Place and Duration of Study: This study was conducted at the Department of General Medicine of Nishtar Hospital Multan from August 2018 to May, 2019.

Materials and Methods: Fifty two patients were equally divided into two groups; control group which received no antiplatelet drug and clopidogrel group in which group patients were prescribed clopidogrel at 75mg daily dose. All the patients were discharged on medication and were followed for a minimum of six months. Age, gender, underlying comorbidities including diabetes mellitus, hypertension, ischemic stroke and dyslipidemias, and incidence of upper GI bleed were compared between the two groups. Student's t test and Chi square test were applied accordingly. P ≤0.05 was considered statistically significant.

Results: Age, gender distribution and history of comorbidities including ischemic stroke, hypertension, diabetes mellitus and dyslipidemias were not significantly different between the two groups (p>0.05). Till the end of study, upper gastrointestinal bleeding was reported in 5 (19.2%) patients of the control group while it was reported in 12 (46.1%) patients of clopidogrel group and the difference in the outcome was statistically significant (p=0.039).

Conclusion: There was significantly greater occurrence of upper GI bleed among the patients taking clopidogrel during the study duration whereas less number of patients from the control group presented with upper GI bleed.

Key Words: clopidogrel, ischemic heart disease, cirrhosis, upper gastrointestinal (GI) bleed.

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INTRODUCTION

Complex changes including defects in platelet function, thrombocytopenia, decreased pro coagulant as well as anticoagulant proteins and altered fibrinolytic systems are associated with cirrhosis. All these changes result in increased bleeding tendency. Prothrombin time (PT) and Activated partial thromboplastin time (aPTT) show hypocoagulablity. However, it has been observed in clinical experience that despite significant alterations in the hemostasis of a patient with cirrhosis, the system maintains a balance by proportionate change in anti- or pro-hemostatic pathways. But this rebalanced hemostatic system of cirrhotic individuals is more friable as compared to the hemostasis in healthy individuals. Cirrhotic individuals are prone to experience thrombotic complications as well as bleeding [1-3].

It was believed that cirrhotic patients were protected against ischemic heart diseases as they were thought to be auto anticoagulated and, therefore, antithrombotic therapy was minimally given in the past. Nowadays, various thrombotic complications including arterial thrombosis, venous thrombosis and portal vein thrombosis are suspected to happen in patients with liver cirrhosis [4-6]. The incidence of these complications is suspected to rise as there has been observed a recent rise in the prevalence of liver cirrhosis and longer survival times in cirrhotic patients. Various anti-thrombotic agents used include heparins, vitamin k antagonists and antiplatelet agents. Antiplatelet agents include aspirin, clopidogrel and ticlopidine.

Use of aspirin for preventing cardiovascular events is associated with peptic ulcer disease and subsequent bleeding [7]. Patients having previous history of peptic

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ulcer disease, taking combined aspirin and clopidogrel or large doses of aspirin, taking other anticoagulant drugs, NSAIDs or steroids drugs, or having Helicobacter pylori infection are at high risk of aspirin-induced peptic ulcer bleeding [8,9]. Other anti-platelet agent is clopidogrel which prevents platelet aggregation and it does not inhibit formation of prostaglandins and functions of cyclooxygenase. Clopidogrel is known to cause less upper gastrointestinal bleed and has higher cardiovascular safety. This drug is a substitute to aspirin for avoidance of secondary cardiovascular events in the patients who either have aspirin allergy or have experience of aspirin related gastrointestinal adverse effects in the past [12]. However, the safety of clopidogrel is documented to be not enough in aspirin related peptic ulcer bleeding as t causes recurrent upper GI bleeding [10, 11]. Clopidogrel or aspirin related upper GI bleed can be well decreased by giving proton pump inhibitors [10, 12-14].

Limited studies have been carried out in the past to assess the factors leading to gastrointestinal bleeding in the patients who were using clopidogrel. Other co-existing factors such as use of other drugs and underlying comorbidities were considered to aid in increased risks of GI bleeding. We are conducting this study in a group of known cases of ischemic heart disease as well as cirrhosis, to evaluate the hazard of upper GI bleeding in the clopidogrel users as compared to patients taking no anti-platelet agents. The purpose of this study is to solely assessthe role of clopidogrel in causing upper GI bleed in ischemic heart disease patients simultaneously suffering from cirrhosis.

MATERIALS AND METHODS

It is a randomized controlled trial conducted in the Department of General Medicine of Nishtar Hospital Multan over a time period of 10 months extending from August 1st, 2018 to May 31st, 2019. Patients were selected using non-probability consecutive sampling technique after calculating sample size from the reference study [15]. We included 52 patients who were simultaneously suffering from ischemic heart disease as well as liver cirrhosis and had at least one episode of upper GI bleed. No age limit was defined. All the patients who has hematological malignancy, coagulopathy, gastrointestinal tract malignancy, gastroenteritis, or inflammatory bowel disease were not included the study.

Ethical approval was obtained from the hospital ethical review board. Informed consent was signed by all the patients before commencement of the study. All the patients were equally divided into two groups using lottery system. One group was control group and no antiplatelet drug was given to this group. Other group was the clopidogrel group. The patients of this group were prescribed clopidogrel at 75mg daily dose. Age, gender were documented before the start of the study. Complete history was taken, after which general physical examination was done. Baseline blood investigations and fasting lipid profiles were done. Any underlying comorbidity such as diabetes mellitus, hypertension, ischemic stroke and dyslipidemias was also documented. Proper treatment for cirrhosis was given. All the patients in both the groups were discharged on oral medication and were followed for a minimum of six months. During this time period, all the patients continued their prescribed medication. All the patients were advised to report immediately if there was blood in vomitus or melena. Patients were also to report if they had any type of emergency. Final outcome of this study was the incidence of upper GI bleed in both the groups.

Age, gender, underlying comorbidities including diabetes mellitus, hypertension, ischemic stroke and dyslipidemias were compared between the two groups. Student's t test was applied to compare the age. Gender and prevalence of comorbidities were compare by applying Pearson chi square test. Outcome was the incidence of upper GI bleed and it was compared between the two groups with Chi square test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Mean age of the control group was 56.77 ± 8.99 years while of the clopidogrel group was 58.27 ± 8.40 years (p=0.537). Control group included 15 males and 11 females while clopidogrel group included 17 males and 9 females (p=0.569). History of ischemic stroke was present in 50% patients of the control group and 30.7% patients of clopidogrel group (p=0.158). Hypertension was positive in 38.5% patients of the control group and 46.1% patients of clopidogrel group (p=0.575).

Table No.1: Baseline and outcome characteristics of the control and clopidogrel groups

Variable	Control (n = 26)	Clopidogrel (n = 26)	p-value
Age, years (mean ± S.D)	56.77 ± 8.99	58.27 ± 8.40	0.537
Gender (male/female)	15 / 11	17 / 9	0.569
Comorbidities, N (%)			
Ischemic stroke	13 (50.0)	8 (30.7)	0.158
Hypertension	10 (38.5)	12 (46.1)	0.575
Diabetes mellitus	11 (42.3)	8 (30.7)	0.388
Dyslipidemias	7 (26.9)	11 (42.3)	0.244
Upper GI bleed, N (%)	5 (19.2)	12 (46.1)	0.039

History of diabetes mellitus was present in 42.3% patients of the control group and 30.7% patients of clopidogrel group (p=0.388). Complete lipid profile showed dyslipidemias in 26.9% patients of the control

group and 42.3% patients of clopidogrel group (p=0.244). Till the end of study, upper gastrointestinal bleeding was reported in 5 (19.2%) patients of the control group while it was reported in 12 (46.1%) patients of clopidogrel group and the difference in the outcome was statistically significant (p=0.039). Table-I

DISCUSSION

In our study, it was observed that the incidence of upper GI bleed became significantly higher with the use of clopidogrel by the ischemic heart disease patients also having cirrhosis. Clopidogrel is prescribed as an alternative to aspirin for primary as well as secondary prevention of cardiovascular events in the patients who have already experienced peptic ulcer bleeding or peptic ulcer disease with aspirin use. Significant risk factors for upper GI bleed in clopidogrel users is the concomitant use of aspirin or peptic ulcer bleed. Previous studies have shown that there are increased risks of peptic ulcer bleed in the patients who are using aspirin along with clopidogrel or have a recent history of peptic ulcer bleed. Clopidogrel is not considered to be safe to use in this high risk group of patients as it increases the chances of upper GI bleed [10, 16, 17].

Clopidogrel is known to hinder the healing process of gastric mucosa and that is why peptic ulcer bleeding reoccurs with its use in the patients with previously healed peptic ulcer disease[10,11,18]. There has been no increased in the risk of upper GI bleed in the CKD patients [19, 20]. In patients using clopidogrel, no effect of H. pylori infection or eradication has been observed on peptic ulcer bleed [10,11,16]. Ulcer prophylaxis is also another issue. PPIs have significant role in preventing peptic ulcers but no significant role of H2RAs has been observed [21]. NHI has limited the use of PPIs in the patients with peptic ulcer disease for a minimum of 4 months [22, 23].

Owing to the great risk of upper GI bleed, aspirin is absolutely contraindicated in patients of cirrhosis [24]. Although very rare at low doses, aspirin usage can precipitate hyponatremia, diuretic resistance and acute renal failure in the patients having ascites [25]. As the incidence of NAFLD is increasing, the demand for anti-platelet therapy for secondary prevention following coronary stenting has been increasing. In the light of recently available evidence, aspirin is thought to be safe in the patients who have cirrhosis but have not developed any varices yet [26]. Aspirin use has also been observed to be associated with the first variceal bleed in the patients who have already developed esophageal varices. Therefore, aspirin is contraindicated in primary as well as secondary prevention in the patients who have already developed varices.

P2Y12 receptor antagonists have recently become popular in the primary as well as secondary prevention of arterial thrombosis. These drugs act by blocking the ADP induced aggregation of the platelets. Clopidogrel in irreversible P2Y12 receptor antagonist. Drug interactions and genetic variations complicate the use of anti-platelet agents and treatment shows various reactions[27]. These agents need to be metabolically activated by the liver and pharmacokinetics cannot be predicted in the patients having cirrhosis. In Child A or B cirrhosis, there is no change in pharmacodynamics and pharmacokinetics of clopidogrel. However, cholestatic jaundice and significant liver damage are labelled as contraindications for the use of clopidogrel, on the package insert.

CONCLUSION

There was significantly greater occurrence of upper GI bleed among the patients who were given clopidogrel during the study duration whereas less number of patients from the control group presented with upper GI bleed. The patients who simultaneously suffer from ischemic heart disease and cirrhosis, should not be prescribed anti-platelet drug, clopidogrel. The frequency of upper GI bleed with clopidogrel use in the cirrhotic patients points towards the fact that these patients are already auto anti-coagulated due to loss of liver function.

Author's Contribution:

Concept & Design of Study:	Muhammad Mumtaz Ather
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost 2015;41(5):468-473.
2. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116(6):878-85.
3. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Eng J Med 2011;365(2):147-56.
4. Tripodi A, Anstee QM, Sogaard KK, Primignani M, Valla DC. Hypercoagulability in cirrhosis: causes and consequences. J Thromb Haemost 2011;9(9):1713-23.
5. Northup PG, Sundaram V, Fallon MB, Reddy KR, Balogun RA, Sanyal AJ, et al. Coagulation in Liver

Disease Group. Hypercoagulation and thrombophilia in liver disease. J Thrombos Haemost 2008;6(1):2-9.
6. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. Coagulation in Liver Disease Study Group. Hemostasis and thrombosis in patients with liver disease: the ups and downs. J Hepatol 2010;53(2):362-71.
7. Luo JC. Gastroprotective strategy in aspirin users. J Chin Med Assoc 2009;72(7):343-45.
8. Laine L. gastrointestinal bleeding with low-dose aspirin–what's the risk?. Aliment Pharmacol Ther 2006;24(6):897-908.
9. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Curr Med Res Opin 2007;23(1):163-73.
10. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Eng J Med 2005;352(3):238-44.
11. Lai KC, Chu KM, Hui WM, Wong BC, Hung WK, Loo CK, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006;4(7):860-65.
12. Huang KW, Luo JC, Leu HB, Huang CC, Hou MC, Chen TS, et al. Risk factors for upper gastrointestinal bleeding in coronary artery disease patients receiving both aspirin and clopidogrel. J Chin Med Assoc 2013;76(1):9-14.
13. Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterol 2010;138(1):82-88.
14. Lanas A, García-Rodríguez LA, Arroyo MT, Bujanda L, Gomollón F, Forné M, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007;102(3):507-15.
15. Lin CC, Hu HY, Luo JC, Peng YL, Hou MC, Lin HC, et al. Risk factors of gastrointestinal bleeding in clopidogrel users: a nationwide population-based study. Aliment Pharmacol Ther 2013;38(9): 1119-28.
16. Ng FH, Wong SY, Chang CM, Chen WH, Kng C, Lanas AI, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. Aliment Pharmacol Ther 2003;18(4):443-49.
17. Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. Am J Cardiol 2008;101(7):960-66.
18. Luo JC, Huo TI, Hou MC, Lin HY, Li CP, Lin HC, et al. Clopidogrel delays gastric ulcer healing in rats. Eur J Pharmacol 2012;695(1-3):112-19.
19. Luo JC, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC, et al. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. CMAJ 2011;183(18):E1345-51.
20. Luo JC, Leu HB, Hou MC, Huang KW, Lin HC, Lee FY, et al. Nonpeptic ulcer, nonvariceal gastrointestinal bleeding in hemodialysis patients. Am J Med 2013;126(3):264-e25-32.
21. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterol 2011;140(3):791-98.
22. Luo JC, Leu HB, Hou MC, Huang CC, Lin HC, Lee FY, Chang FY, Chan WL, Lin SJ, Chen JW. Cirrhotic patients at increased risk of peptic ulcer bleeding: a nationwide population-based cohort study. Alimentary pharmacology & therapeutics 2012;36(6):542-50.
23. Peng YL, Leu HB, Luo JC, Huang CC, Hou MC, Lin HC, et al. Diabetes is an independent risk factor for peptic ulcer bleeding: A nationwide population-based cohort study. J Gastroenterol Hepatol 2013;28(8):1295-9.
24. Miser WF. Appropriate aspirin use for primary prevention of cardiovascular disease. Am Fam Physician 2011;83(12):1380-86.
25. European Association For The Study Of The Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53(3):397-417.
26. Russo MW, Pierson J, Narang T, Montegudo A, Eskind L, Gulati S. Coronary artery stents and antiplatelet therapy in patients with cirrhosis. J Clin Gastroenterol 2012;46(4):339-44.
27. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J 2011;32(23):2922-32.
28. Cattaneo M. New P2Y12 inhibitors. Circulation 2010;121(1):171-179.