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Ticagrelor Use in Indian Patients Undergoing Neuroendovascular Procedures: A Single Center Experience

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Purpose: A safe and efficacious antiplatelet drug is needed for patients with clopidogrel resistance who undergo neuroendovascular procedures. Ticagrelor is a new reversibly binding, oral, direct-acting P2Y receptor antagonist with no known resistance. We describe our clinical experience using ticagrelor for neuroendovascular procedures in Indian patients with clopidogrel resistance at the NH Institute of Neurosciences, Narayana Health City, Bangalore.

Materials and Methods: We retrospectively reviewed our endovascular procedure database for all patients with predefined clopidogrel resistance. Clopidogrel resistance was defined as P2Y12 inhibition <40%. Patients were administered ticagrelor along with aspirin prior to the procedure.

Results: Of 127 patients, 32 (25%) were non-responders to clopidogrel (22 [69%] males, 10 [31%] females; median age, 54 years [range, 20–75]). All patients were treated with a 180-mg loading dose of ticagrelor, followed by 90 mg twice daily. Twenty patients (63%) underwent endovascular intervention for intracranial aneurysm, two (6%) for dissecting aneurysms, nine (28%) for stenotic lesions, and one (3%) for carotico-cavernous fistula. No patient experienced any adverse effects related to the use of Ticagrelor in the postoperative period.

Conclusion: Ticagrelor is an effective alternative to clopidogrel for use in conjunction with aspirin in patients with clopidogrel resistance. None of our patients had adverse effects from ticagrelor. Drug cost, twice-daily dosing, and risk of faster platelet aggregation activation after discontinuation should be taken into consideration prior to its use in such patients.

Key Words: Clopidogrel; Ticagrelor; Endovascular procedures; Stents

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INTRODUCTION

New advances in intracranial or extracranial stents, stent grafts, flow diverters, and pCONUS have changed the way in which patients are treated in the field of neurointervention. The endovascular use of these devices requires dual antiplatelet therapy due to the inherent risk of platelet-rich in-stent thrombus formation.[1-3] The importance of dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist (such as clopidogrel, prasugrel, or ticagrelor) during stenting has been documented in numerous studies.[4-6] The combination of aspirin and clopidogrel has been documented to be safe and efficacious as compared to other antiplatelet combinations.[7-10] While aspirin resistance is less common,

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clopidogrel resistance may be more challenging, as it is reported to be as high as 30–35% and is reported to increase thromboembolic complications, even with escalating dosing of clopidogrel.[11-14]

In recent years, a few studies on patients after neurovascular stent placement have revealed similar rates of resistance for aspirin and clopidogrel compared with rates in the cardiovascular literature.[13,15-17] This necessitates the need to look for a safe and efficacious antiplatelet regimen that not only minimizes the risk of neurosurgical thromboembolism after stenting but also reduces risk of perioperative intracranial hemorrhage due to potent P2Y12 receptor over-inhibition.

Unlike clopidogrel, ticagrelor is a reversible allosteric binder that does not need hepatic activation. Ticagrelor and its equipotent metabolite are absorbed quickly and reach peak concentration after about 1.5 hours.[18] Moreover, the extremely low number of non-responders makes it particularly advantageous for neurological stenting procedures.[19-22]

The purpose of this paper is to present our experience using ticagrelor in combination with aspirin in a limited cohort of Indian patients with clopidogrel resistance who underwent elective neuroendovascular procedures at the NH Institute of Neurosciences (Narayana Health City, Bangalore).

MATERIALS AND METHODS

Study design

All the patients undergoing intracranial or extracranial neuroendovascular stenting at the NH Institute of Neurosciences received a loading and maintenance antiplatelet drug dose as per a predefined medication regimen. Patients got tested for aspirin and clopidogrel resistance using light aggregometry and underwent follow-up neurovascular imaging with cerebral angiography at the end of 3 months. Their clinical, procedural, and follow-up data were prospectively collected and entered into a neurointervention procedure database.

The present retrospective study was conducted with approval by the Institutional Ethics Committee of NH Institute of Neurosciences, Narayana Health City, Bangalore. We screened our database for the period from July 2015 to March 2017, and all patients with documented clopidogrel resistance who were then shifted to a ticagrelor and aspirin regimen were included in the study. Detailed information was collected, including clinical assessment, indication for stent placement, procedural information, light aggregometry results, complications and adverse events during admission and follow up, follow-up neuroimaging results, and duration of ticagrelor therapy. Of these, patients lost to follow up or with incomplete clopidogrel test results were excluded from the analysis.

Complications that were monitored and documented in the database included 30-day thromboembolic events (stroke or myocardial infarction) and bleeding. Bleeding events were classified as per the A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of Ticagrelor Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes (PLATO- a Study of PLATelet Inhibition and Patient Outcomes) trial criteria into major life-threatening, other major bleeding, and minor bleeding.[23] Patients were also monitored for dyspnea, bradyarrhythmias, diarrhea, and diarrhea and increase in serum creatinine.

Medication protocol

All patients undergoing intracranial or extracranial neuroendovascular stenting at the NH Institute of Neurosciences received either a loading dose of 300 mg clopidogrel and 325 mg aspirin 1 day prior to the procedure or 75 mg clopidogrel and 150 mg aspirin daily for 7 days before the procedure. All patients were subjected to a light transmission aggregometry test; and if it was found that they were non-responders to clopidogrel, they were started on a loading dose of 180 mg ticagrelor orally, followed by a maintenance dose of 90 mg twice daily. These patients also received heparin anticoagulation during the procedure with an activated clotting time maintained above 250 seconds for the duration of the procedure. All patients received ticagrelor for a period of 3 months.

Platelet function testing

At the NH Institute of Neurosciences, aggregation studies were done with a platelet aggregometer using a light aggregometry technique after 6 hours of a loading dose or after 7 days of antiplatelet treatment in elective cases. Non-responders were defined as those with <40% reduction in platelet aggregation inhibition, as per the parameters observed by our institutional laboratory.

Statistical analysis

Descriptive statistical analysis was done using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA)

and results were summarized as mean and median for continuous data and as proportion for frequency data.

RESULTS

From July 2015 to May 2017, of the total 127 patients who underwent a neuroendovascular procedure, 32 patients (25%) were identified as non-responders to clopidogrel and were started on a ticagrelor and aspirin regimen. There were 22 men (69%) and 10 women (31%), with a median age of 54 years (range, 20–75). All procedures were elective. Twenty patients (63%) underwent endovascular intervention for intracranial aneurysm (three bled and 17 unbled), two (6%) for dissecting aneurysms, nine (28%) patients for stenotic lesions, and one (3%) patient for carotico-cavernous fistula (CCF). Of the 20 patients with aneurysms, 11 patients (55%) were treated with flow diverters and nine patients (45%) had stent-assisted coiling. All stenotic lesions were stented, and CCF lesions underwent stent grafting. These results are summarized in Tables 1, 2.

There were no thromboembolic phenomena (stroke or myocardial infarction) during follow up. There was no incidence of major, minor, or life-threatening bleeding. No patient had dyspnea, diarrhea, dizziness, bradyarrhythmia, or increased serum creatinine. Follow-up angiography revealed no in-stent thrombosis or stenosis.

Table 1. Clinical characteristics of clopidogrel non-responders for the neuroendovascular procedure

Variable	Value
Total number of patients	32
Sex	
Male	22 (69)
Female	10 (31)
Age (years)	
Median	54
Range	20–75
Age distribution (years)	
20–29	2
30–39	2
40–49	7
50–59	13
60–69	7
>70	1

Values are presented as number (%).

DISCUSSION

A clopidogrel and aspirin dual antiplatelet regimen has been routinely used for coronary intervention, and off-label use of this drug combination has been standard for neuroendovascular procedures. Because of the complex pathophysiology of cerebrovascular thromboembolic events involving thrombosis, inflammation, vascular biology, and hemodynamics, no single agent can be expected to completely stop ischemic events.

Clopidogrel resistance is defined as the failure of a molecule to inhibit the target of its action; it has been observed in approximately one-third of patients. It is best demonstrated by the evidence of residual post treatment P2Y12 activity by

Table 2. Neuroendovascular procedures carried out in clopidogrel non-responders after ticagrelor administration

Variable	Value
Type of procedure	
Elective	32 (100)
Indication for procedure	
Aneurysm	20 (63)
Paraophthalmic ICA	7
Supraclinoid ICA	6
Cavernous ICA	2
Middle cerebral artery	3
Anterior cerebral artery	1
Vertebral artery	1
Dissecting aneurysms	2 (6)
Arterial stenosis	9 (28)
Carotico-cavernous fistula	1 (3)
Type of aneurysmal procedure	20
Flow diverter	11 (55)
Pipeline Embolisation Device	1
p64	7
Silk	2
XCalibur	1
Stent assisted coiling	9 (45)
Solitaire AB	6
Leo+	3

Values are presented as number (%).
ICA, internal carotid artery.

measuring adenosine diphosphate (ADP)-induced platelet aggregation before and after treatment. No single receptor signalling pathway is responsible for its activity. Therefore, a single treatment strategy may not be sufficient to overcome clopidogrel resistance.[24] A limited number of studies on clopidogrel resistance in India have been carried out on patients with acute coronary syndrome and coronary artery disease; they indicate that prevalence of clopidogrel resistance in India is aligned with the global incidence.[25,26] Observational studies from the cardiovascular literature have demonstrated a relationship between clopidogrel resistance and the development of cardiovascular events after percutaneous coronary intervention.[27,28] Fifi et al.[11] reported increased peri-procedural thromboembolic complications from neurovascular stent-placement procedures in their patients with clopidogrel resistance.

Ticagrelor is the first reversibly binding, oral, direct-acting P2Y receptor antagonist. Clinical pharmacology and early dose-finding studies have suggested a faster onset and greater inhibition of platelet aggregation with ticagrelor than with clopidogrel.[29,30] In the ONSET-OFFSET trial, ticagrelor achieved a rapid and better platelet inhibition compared to clopidogrel.[31] Unlike clopidogrel, ticagrelor and its metabolite are primarily metabolized via the CYP34A enzyme and, hence, do not require hepatic activation. Also, the extremely low number of non-responders makes it particularly advantageous for neurological stenting procedures.[19-22] In the PLATO trial and its sub-analyses, use of ticagrelor achieved platelet inhibition in almost all cases of clopidogrel resistance, had lower incidences of in-stent thrombosis, and had similar rates of major and fatal bleeding.[32-34] However, there is limited data documenting the use of ticagrelor in patients undergoing neurointerventional procedures. Hanel et al.[35] documented the safety and efficacy of ticagrelor when used in conjunction with aspirin as a dual treatment in their patients with clopidogrel resistance.

We present our experience using ticagrelor in Indian patients undergoing neurointerventional procedures who were non-responders to clopidogrel. At the NH Institute of Neurosciences, we have seen a few in-stent thromboses arise from aspirin and clopidogrel dual antiplatelet therapy. Since we started testing patients for clopidogrel resistance and moved non-responders to ticagrelor in conjunction with aspirin, we have not encountered any complications to date. All our patients tolerated ticagrelor well with no incidence of any adverse event including hemorrhage. Our study is, however, limited by having a small number of patients and a retrospective nature. A future prospective, randomized, and larger patient population study is warranted to support the safety of ticagrelor in neurointerventional procedures, especially as newer technology with interventional devices is evolving so quickly.

CONCLUSION

In summary, we report the safety and efficacy of ticagrelor when used in conjunction with aspirin in a small group of Indian patients who were non-responders to clopidogrel for neuroendovascular procedures at our center. The drawbacks of ticagrelor, including its cost and its risk of faster platelet aggregation activation after discontinuation, should be taken into consideration prior to its utilization.

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