CASE SERIES

Safety and efficacy of cangrelor in acute stenting for the treatment of cerebrovascular pathology: preliminary experience in a single-center pilot study

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ABSTRACT

Background Treatment of acute cerebrovascular pathology, such as acute ischemic stroke or intracranial aneurysms, presents a challenge if an extracranial or intracranial stent is required; immediate platelet inhibition is vital. To date, there is no standardized approach for antiplatelet inhibition in an acute setting.

Objective To report our preliminary experience and lessons learnt using cangrelor in acute neurointervention.

Methods A single-arm pilot study was performed to assess the safety and efficacy of cangrelor plus aspirin for platelet inhibition in patients who require acute stenting in the setting of neuroendovascular treatment.

Results Eight patients were enrolled between October 2017 and August 2018. Median age was 71 years (53–86). Seven patients were treated in an acute setting according to the stroke protocol at our institution, while one patient was treated for a symptomatic, unruptured aneurysm with flow diversion and coiling. At admission, the median National Institutes of Health Stroke Scale score for the patients with stroke was 12.5 (range 2–22.3). Cangrelor was infused and all patients achieved adequate platelet inhibition (<200 PRU (P2Y12 reaction units)). Six of seven patients with ischemic stroke had a carotid stent placed and one had an intracranial stent deployed in the middle cerebral artery. None of the patients experienced intraprocedural thromboembolic complications, intraprocedural in-stent thrombosis, hemorrhagic complications, or stroke within 24 hours after the intervention. The majority of patients (6/8) had a good clinical outcome at discharge (modified Rankin Scale score 0–2).

Conclusions Our findings suggest that cangrelor is a promising alternative in acute stenting for the treatment of cerebrovascular pathology. However, further studies with larger samples are required to accurately elucidate its safety and effectiveness in neuroendovascular procedures.

INTRODUCTION

Dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor), has become the standard regimen to decrease the rate of thromboembolic complications in patients who undergo any intracranial or extracranial stenting. In the acute setting, such as acute ischemic stroke or subarachnoid hemorrhage (SAH), if stenting is necessary, immediate platelet inhibition is desired. This situation is not uncommon in the setting of ischemic stroke owing to tandem occlusion (~10%) or secondary to intracranial atherosclerotic disease (~8–10%).[1 2] It is also necessary when dealing with stenting or flow diversion in patients with SAH.[3 4]

Oral antiplatelet agents such as prasugrel and ticagrelor provide faster and more potent P2Y12 antagonism than clopidogrel; however, all of them have a slow offset of activity, which is a problem if the patient needs urgent surgery (table 1). To date, there is no standard antiplatelet management when acute stenting is required in neurointervention. Cangrelor has been assessed in the setting of acute coronary intervention in three different phase III clinical trials,[5–7] which compared it with other antiplatelet agents. Administration of cangrelor is intravenous facilitating the onset and offset activity.

Cangrelor (Kengreal, Chiesi USA) is a new potent P2Y12 receptor antagonist. It is a non-thienopyridine ATP analog, which reversibly and directly inhibits the P2Y12 receptor. It is administered intravenously and it has a rapid onset and offset with a half-life of 3–6 min. It does not require transformation to active metabolites and is given as a bolus plus an infusion, providing immediate and consistent platelet inhibition. Cangrelor is deactivated rapidly by dephosphorylation to its primary metabolite, a nucleoside, which has no antiplatelet activity, and the platelet function is normalized within 1 hour after discontinuation.[8 9] This unique feature is especially useful for patients undergoing neurointervention, with the possibility of having the drug essentially out of the system if any unexpected intervention/surgery is needed. Cangrelor was approved by the US Food and Drug Administration in 2015 as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis. Previous studies have shown the benefit of cangrelor over clopidogrel with fewer thromboembolic complications in patients undergoing PCI. However, the results may not be readily applicable to patients who require neurointervention since no literature assessing use of this drug in our field has been published. Herein, we report our preliminary experience and lessons learnt using cangrelor in acute neurointervention.

Table 1 Pharmacological characteristics of P2Y12 receptor inhibitors and GP IIb/IIIa inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab	Eptifibatide	Tirofiban
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine	ATP analog	GPIIb/IIIa i	GPIIb/IIIa i	GPIIb/IIIa i
Reversibility	Irreversible	Irreversible	Reversible	Reversible	Irreversible	Irreversible	Irreversible
Prodrug	Yes	Yes	No	No	Monoclonal antibody	Peptide	Non-peptide
Administration route	Oral	Oral	Oral	Intravenous	Intravenous	Intravenous	Intravenous
Onset of effect	2–8 hours	30 min to 4 hours	30 min to 4 hours	Immediate	10 min	15 min	30 min
Duration of effect	5–7 days	7–10 days	3–5 days	30–60 min	12 hours	4–6 hours	4–8 hours
Half-Life	~6 hours	~7 hours	~8 hours	3–5 min	30 min	1–3 hours	1–2 hours
Frequency	Once daily	Once daily	Twice daily	Bolus plus infusion	Bolus plus infusion	Bolus plus infusion	Bolus plus infusion
Influenced by genetic variation	Yes	No	No	No	No	No	No
Approved settings	ACS (invasively and noninvasively treated) and PCI in stable CAD	ACS undergoing PCI	ACS (invasively and noninvasively treated)	*PCI in patients with ACS and stable CAD	ACS undergoing PCI	ACS (invasively and noninvasively treated)	ACS (invasively and noninvasively treated)

Source: Adapted from Qamar and Bhatt.[9]
*Patients with ACS or stable CAD who have not been pretreated with P2Y12 receptor inhibitor and are not receiving a glycoprotein IIb/IIIa inhibitor.
ACS, acute coronary syndrome; ATP, adenosine triphosphate; CAD, coronary artery disease; GPIIb/IIIa i, Glycoprotein IIb/IIIa inhibitor; PCI, percutaneous coronary intervention.

MATERIALS AND METHODS

Objective and design

The aim of this study was to assess in neurointervention the safety and efficacy of cangrelor plus aspirin for platelet inhibition in patients who require acute stenting in the setting of ischemic stroke or aneurysm treatment. The study was approved by the Baptist Medical Center institutional review board (#17–64). Enrolled patients or their surrogates provided written informed consent.

Patient population

Patients were eligible for inclusion in the study if they were at least 18 years of age and presented to the hospital with acute ischemic stroke (secondary to tandem occlusion or intracranial atherosclerotic disease) or symptomatic intracranial aneurysm, underwent emergent cerebral angiography, and required acute stenting. Patients were excluded from the study if any of the following criteria were present: (1) use of any P2Y12 inhibitor at any time within the 7 days preceding the procedure, (2) eptifibatide or tirofiban usage within 12 hours preceding the procedure (most recent dose must have been administered ≥12 hours previously), (3) abciximab usage within 7 days preceding the procedure, (4) international normalized ratio >1.5, or (5) participation in another clinical trial.

Cangrelor administration protocol

Patients undergoing endovascular treatment who required acute stenting were assigned to receive a loading dose of 325 mg of aspirin plus a 15 µg/kg bolus, followed by a 2.0 µg/kg/min IV infusion of cangrelor for a minimum of 2 hours or until conclusion of the index procedure, unless continued IV therapy was deemed necessary by the treating physician. We chose to use half of the cardiac dose of cangrelor based on previous experience with other IV agents such as eptifibatide, in which half of the cardiac dose provided the protection needed for neurovascular cases. The P2Y12 response was evaluated with the VerifyNow test (Accriva Diagnostics, San Diego, USA). After the intervention, all patients were maintained by standard dual antiplatelet therapy. The transition to oral P2Y12 inhibitor occurred at any time during the cangrelor infusion. It consisted of a loading dose of ticagrelor 180 mg. The endovascular treatment, and the post-procedure dual antiplatelet therapy, was decided on a case-by-case basis by the neurointerventionalists.

Follow-up

Follow-up visits were scheduled according to our standard clinical practice and the treating physician's judgment. They consisted of clinical visits at 30 days, 3–6 months, and yearly thereafter, depending on the cerebrovascular pathology treated.

Study outcomes

The primary endpoints were the incidence of intraprocedural thromboembolic complications, intraprocedural in-stent thrombosis, and the composite rate of ischemic stroke or intracranial hemorrhage at 24 hours. Secondary endpoints consisted of the composite primary outcome at 7 days, and 30 days after the procedure, in-stent thrombosis at 48 hours after the intervention, incidence of transient ischemic attack within 30 days, and the all-cause mortality rate.

Statistical analysis

Demographic data and baseline characteristics are presented as mean or median for continuous variables, as appropriate, and absolute values and percentages for categorical variables. For this preliminary report, only descriptive statistics were performed. Statistical analysis was performed using Stata software, V.14 (StataCorp, College Station, Texas, USA).

RESULTS

Eight patients were enrolled in our study between October 2017 and August 2018. Seven patients presented to our center with an acute ischemic stroke due to tandem occlusion or cervical internal carotid artery obstruction alone. The baseline characteristics are summarized in table 2. Overall, the median age was 71 years (range 53–86). The majority of patients had a good modified Rankin Scale (mRS) score of 0–2 before their stroke. At admission, the median National Institutes of Health Stroke Scale score was 12.5 (range 2–22.3) for the patients with stroke. All the patients were treated in an acute setting based on our stroke protocol. Two of the seven patients with acute stroke

Table 2 Baseline characteristics

Subject	Age	Baseline NIHSS	Pre-stroke mRS	Comorbidities	Core	Tmax>6s	Tandem	Site of Occlusion
1	80's	18	0	Hypertension	0	15	No	Cervical LICA
2	50's	7	4	Hypertension DM Peripheral Vasc Previous stroke Smoker	0	167	Yes	RICA-terminus RM1
3	60's	23	0	Hypertension Previous stroke	N/A	N/A	Yes	Cervical LICA LM1
4	80's	22	2	Hypertension DM CAD Hyperlipidemia	N/A	N/A	Yes	Cervical RICA RM1
5	50's	2	0	None	0	82	No	Cervical RICA
6	80's	2	0	Hyperlipidemia	0	38	Yes	Cervical RICA RM1
7	70's	18	1	Hypertension Hyperlipidemia DM Smoker	6	141	Yes	Cervical RICA RM1
Subject	**Age**	**Pre-event mRS**	**GCS**	**Hunt-Hess Scale**	**Modified Fisher Scale**	**WFNS SAH Scale**	**Comorbidities**	**Aneurysm Location and size**
8	60's	0	15	0	0	1	Hypertension	Left Sup Hypophyseal 5 x 4 mm

*Core and Tmax>6s were obtained with computed tomography perfusion using the RAPID Software (iSchemaView, Menlo Park, CA).
CAD, coronary artery disease; DM, Diabetes Mellitus type 2; F, female; GCS, Glasgow Coma Scale; LICA, left internal carotid artery; LM1, left middle cerebral artery M1 segment; M, male; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RICA, right internal carotid artery; RM1, right middle cerebral artery M1 segment; SAH, Subarachnoid Hemorrhage; Sup, Superior; V4, vertebral artery, V4 segment; WFNS, World Federation of Neurological Surgeons.

received IV tissue plasminogen activator. Cangrelor was infused and all patients achieved adequate platelet inhibition (<200 PRU (P2Y12 reaction units)). Six of the seven patients with ischemic stroke had a carotid stent placed and only one had an intracranial stent deployed in the middle cerebral artery (table 3). None of the patients experienced intraprocedural thromboembolic complications, intraprocedural in-stent thrombosis, or stroke within 24 hours after the intervention. All the patients obtained a good Thrombolysis in Cerebral Infarction score (2b/3). The majority of patients (5/7) had a good clinical outcome at discharge (mRS score 0–2).

One sexagenarian patient presented with a symptomatic, unruptured hypophyseal artery aneurysm. This patient had progressively worsening visual deficits but no other neurologic abnormalities or altered mental status. Baseline characteristics of this patient as well as Glasgow Coma Scale, Hunt-Hess scale, modified Fisher scale and World Federation of Neurological Surgeons SAH scale scores are summarized in table 2. The

Table 3 Procedural characteristics and clinical status at discharge

Subject	Intervention	Adjuvant Device	Approach	P2Y12 after Cangrelor Infusion	Ischemic Stroke or Intracranial Hemorrhage at 24 hours	Intraprocedural Thromboemcolic Complications	Intraprocedural In-stent Thrombosis
1	Carotid Stenting	X-act stent (cervical LICA)	N/A	114	No	No	No
2	Thrombectomy Intracranial Stenting	Solitaire (RICA-terminus) Enterprise (RM1)	Retrograde	118	No	No	No
3	Carotid Stenting Thrombectomy	X-act stent (cervical LICA) Trevo (LM1)	Anterograde	118	No	No	No
4	Carotid Stenting Thrombectomy	Trevo (RM1) X-act stent (cervical RICA)	Retrograde	115	No	No	No
5	Carotid Stenting	X-act (cervical RICA)	N/A	140	No	No	No
6	Carotid Stenting Thrombectomy	X-act (cervical RICA) Solitaire (RM1)	Anterograde	74	No	No	No
7	Carotid Stenting Thrombectomy	X-act (cervical RICA) Trevo (RM1)	Anterograde	84	No	No	No
8	Flow Diversion + Coiling	PED Flex (LICA)	N/A	53	No	No	No

LICA, Left internal carotid artery; RICA, Right internal carotid artery; LM1, left middle cerebral artery, M1 segment; RM1, right middle cerebral artery, M1 segment; PED Flex, Pipeline Flex Embolization Device

aneurysm was treated in an acute setting with flow diversion (Pipeline Flex Embolization Device; PED Flex, Medtronic, Irvine, California, USA) and coiling. Cangrelor was infused and adequate platelet inhibition (<200 PRU) was achieved. The aneurysm was completely occluded, and post-treatment angiography showed good wall apposition and coil impaction. No intraprocedural thromboembolic complications, intraprocedural in-stent thrombosis, or stroke occurred within 24 hours of intervention. The patient had a good clinical outcome at discharge (mRS score 0).

Primary endpoints

In this preliminary report, none of the patients experienced intraprocedural thromboembolic complications, intraprocedural in-stent stenosis, or stroke within 24 hours after the intervention.

Secondary endpoints

In this preliminary report, none of the patients experienced in-stent thrombosis at 48 hours after the intervention, had a transient ischemic attack, or died.

DISCUSSION

Our preliminary experience using cangrelor suggests it is a promising alternative for platelet inhibition when stenting is required for the treatment of acute ischemic stroke or aneurysm treatment. No evidence of in-stent thrombosis was seen in any of our patients and none of them developed further ischemic strokes. Although our sample is small compared with the cardiology trials, our results are in concordance with the outcomes reported in the PCI studies comparing cangrelor with clopidogrel. Briefly, the three phase III clinical trials assessing the efficacy and safety of cangrelor compared with clopidogrel in patients undergoing PCI were: CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX.

The CHAMPION PCI[6] study was a double-blind, double-dummy, and randomized clinical trial that included 8716 patients. The primary outcome consisted of evaluating death, myocardial infarction, and revascularization at 48 hours. Investigators compared cangrelor (bolus then infusion) with clopidogrel. Results showed that cangrelor was non-inferior to clopidogrel for the incidence of the primary outcome at 48 hours and 30 days.

The second study, the CHAMPION PLATFORM,[5] was also designed as a double-blind, placebo-controlled, randomized clinical trial. Investigators included 5362 subjects and compared cangrelor (bolus then infusion) with clopidogrel in patients undergoing PCI. Results showed no difference between treatments in the primary outcome (death, myocardial infarction, or revascularization at 48 hours) but a reduction in secondary outcomes such as in-stent thrombosis.

In the CHAMPION PHOENIX trial,[7] cangrelor was compared with clopidogrel in 11 145 patients presenting with stable angina, non-ST elevation myocardial infarction, or ST-elevation myocardial infarction who required PCI. The use of cangrelor was shown to significantly reduce the risk of ischemic events, including in-stent thrombosis, at 48 hours and 30 days, with no increase in the risk of severe bleeding across the spectrum of patients undergoing PCI.

Treatment of acute tandem occlusion strokes is especially challenging given the need to deal with both lesions urgently and with timing an important factor for brain tissue salvaging. In addition, there is concern about hemorrhagic transformation in stroke, aneurysm re-rupture, or the hemorrhagic complications of external ventricular drain in these cases, where rapid withdrawal of the antiplatelet agent is beneficial to the patient. In recent years, endovascular thrombectomy has become the standard of care in treating large vessel occlusion strokes in the anterior circulation, but most trials did not evaluate simultaneous extracranial circulation stenosis treatment.[10 11]

It is still controversial whether these extracranial lesions should be managed in the acute setting with angioplasty alone or by stenting.[12] Those who argue in favor of angioplasty alone state that the antiplatelet regimen after stent implantation raises the risk of hemorrhagic complications. Although there is still no agreement about which treatment to choose, in recent years there has been an increase in supporting evidence for the use of stenting for the extracranial portion of the tandem occlusion.[13] The use of stents in the acute setting of a stroke increases the risks of developing intraprocedural thromboembolic complications, thus leading to the use of dual antiplatelet therapy to keep the endovascular construct open.[14] This concern can also be extended to the use of stents and flow diverters in the acute setting for aneurysm treatment, as these cases also require the use of antiplatelet therapy to avoid thromboembolic events.[3] To date, there is no consensus on which antiplatelet regimen to use, with most centers choosing a combination of aspirin plus one of the following: clopidogrel, ticagrelor, or prasugrel. The disadvantage of current antiplatelet options is that most of them have a considerable time window for onset of action and also an undesirable half-life and offset length (table 1).

Furthermore, the fast reversible feature of cangrelor is also of considerable interest in emergent neurointerventional therapy, given the potential risks of hemorrhagic complications after the procedures. These complications, which may require open surgical management with craniotomy or external ventricular drainage, can most certainly benefit from the fast reversal of P2Y12 inhibition offered by cangrelor, leading to a reduction of intraoperative bleeding or further hemorrhagic complications. Another frequently observed situation in which a fast-acting and reversible agent is uniquely useful is as bridging therapy for patients receiving dual antiplatelet therapy and undergoing surgical procedures. Bridging therapy continues to have a controversial benefit during anticoagulation,[15] but for bridging therapy for dual antiplatelet therapy using cangrelor there is significant evidence of feasibility, safety, and efficacy in the cardiology literature.[16 17] Hence, use of cangrelor in the neurointerventional and neurosurgical field needs to be assessed.

However, cangrelor is expensive for the patient and healthcare system, with a higher cost than other available P2Y12 inhibitors. This could be a limiting factor in many practices both country and worldwide.

Once cangrelor is infused or suspended, ticagrelor seems to be the safest alternative, given the lack of interaction between the two drugs .[18] Ticagrelor binds reversibly to the P2Y12 receptor and does not require metabolism to become active.[19] In vitro studies have shown that neither clopidogrel nor prasugrel can bind to the P2Y12 receptor while cangrelor is actively bound to the receptors. In contrast, ticagrelor can be given during or after the infusion, facilitating the bridging between intravenous and oral medication.[20 21]

In summary, the recommendations for the transition to oral P2Y12 receptor antagonists are as follows: (1) clopidogrel (loading dose 600 mg) should be given after the cangrelor infusion is terminated since its antiplatelet effects are blocked if cangrelor is concurrently administered[22 23]; (2) prasugrel (loading dose 60 mg) should be administered 30 min before or at the termination of the cangrelor infusion, thus its active

metabolite persists in the blood sufficiently to allow the overlap of therapy with minimal platelet function recovery[24]; (3) ticagrelor (loading dose 180 mg) may be administered at any time during the cangrelor infusion or once it is terminated since it binds to the P2Y12 receptors in a different way than cangrelor, resulting in consistent platelet inhibition, reducing the gap between intravenous and oral drugs, and limiting the platelet function recovery. This has the theoretical advantage of decreasing the risk of thrombosis.[19]

To our knowledge, this is the first report of using cangrelor for patients undergoing acute neurointervention. Although patients still need to maintain dual antiplatelet therapy after the procedure, cangrelor allowed more predictability and control of P2Y12-receptor antagonism with a faster onset and offset of action.

Limitations

Our study has several limitations. It is only a preliminary report of an ongoing prospective pilot study assessing the safety and efficacy of cangrelor in acute neuroendovascular intervention with limited clinical follow-up. It is a single-arm study with non-blinded assessment and our results reflect a single-center experience, which may not be generalizable to other facilities. This study is clearly underpowered and conclusions are only exploratory and may not represent the final outcome.

CONCLUSIONS

Our findings suggest that cangrelor is a safe, promising alternative antiplatelet agent for acute stenting for the treatment of cerebrovascular pathology. However, further studies with larger samples are required to accurately elucidate its safety and effectiveness in neuroendovascular procedures.

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Competing interests RAH is a consultant for Medtronic, Stryker, Codman, and MicroVention. The remaining authors have nothing to disclose.

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