Low-dose prasgurel versus clopidogrel on the dual antiplatelet regimen for intracranial stenting or flow diverter treatment for unruptured cerebral aneurysms: a multi-center randomized controlled trial

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Background

Unruptured intracranial aneurysm (UIA) is a relatively common disease, with a prevalence of approximately 1% of the total population. It is a fatal hemorrhagic stroke with a mortality of over 30% of all cases of subarachnoid hemorrhage. In the past decade, along with the development of neurointerventional therapy, there has been a breakthrough in the treatment of UIAs. Widely accepted techniques of neurointerventional therapy include coil embolization with or without stent deployment and flow diverter insertion. However, these two techniques inevitably carry a risk of thromboembolism. For prevention and reduction of risk, dual antiplatelet therapy is commonly used clinically.

A dual antiplatelet drug combination therapy comprising aspirin and P2Y12 inhibitors has been the regimen of choice for patients requiring stent insertion in the cardiological and neurovascular fields. However, clopidogrel does not produce normal metabolites due to various internal and external factors in the metabolic process in the liver and eventually fails to perform its primary role of suppressing platelet activity in many situations, called "clopidogrel hyporesponsiveness." A low clopidogrel response has been reported in approximately 5-44% of the total population, which is associated with an increase in thromboembolism. However, there is no standard test that can confirm this, and a standard value for defining a low response has not yet been established.

Accordingly, the demand for next-generation P2Y12 antagonists has continued, and according to a paper published in 2007, clopidogrel and prasugrel patient responses and platelet activity inhibition were compared before percutaneous coronary intervention [1]. Reportedly, the platelet aggregation inhibitory effect is remarkably high. Choi et al. revealed the efficacy of prasugrel in coil embolization of cerebral aneurysms with stent insertion; the incidence of thromboembolism was significantly lower in the prasugrel group than in the clopidogrel group (0.9% vs. 6.4%; P = 0.01), and the bleeding risk was reported to be similar (0.5% vs. 2.2%; P = 0.22) [2,3]. However, these recent studies are based on single-center retrospective data; therefore, there is a limit to the level of evidence.

This study aimed to compare the safety and usefulness of prasugrel vs. clopidogrel in patients scheduled to undergo stent or diverter treatment for unruptured cerebral aneurysms.

Specific Aim and Hypothesis

The primary aim of the present study was to investigate the effect of prasugrel in patients undergoing neurointerventional treatment for UIAs (i.e., stent-assisted coiling or flow diverter insertion). The prasugrel and clopidogrel groups were compared to elucidate their safety (hemorrhagic complications) and efficacy (thromboembolic complications) in the periprocedural period. In the present study, we hypothesized that prasugrel has a preventive effect that is not inferior to that of clopidogrel in any treatment group.

Research Design and Methods

Research Design

Patients who visited the outpatient department of neurosurgery at multiple institutions (Severance Hospital, Gangnam Severance Hospital, Yongin Severance Hospital, Ewha Womans University Seoul Hospital, Bucheon St. Mary's Hospital, and International St. Mary's Hospital) were screened to participate in the present research. After following the study protocol, the participants were divided into the prasugrel and clopidogrel groups by 1:1 randomization.

- Detailed information of the study protocol

1) After patients with UIAs were hospitalized, baseline characteristics were obtained, and blood tests, including renal function test (glomerular filtration rate [GFR]), liver function test (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), and pregnancy test, were performed.
2) Cerebral angiography was performed, and detailed consent was obtained after the study protocol was explained to the participants who met the selection criteria.
3) Using a randomization program, the test group (203 patients; aspirin 100 mg + prasugrel 5 mg) and the control group (203 patients; aspirin 100 mg + clopidogrel 75 mg) were classified.
4) The above drugs were prescribed according to the assigned group and taken 5 days before the procedure.
5) The patients were hospitalized 2 days before the procedure, and whether the drug was taken was checked immediately after hospitalization (if the drug was not taken properly, the patient was excluded from the study).

6) The platelet function test (VerifyNow assay; Accumetrics, San Diego, California, USA) was performed a day before the procedure to check the clopidogrel responsibility and adjust the drug according to the result.

P2Y12 reaction units (PRU) <220

- Clopidogrel group: aspirin 100 mg + clopidogrel 75 mg
- Prasugrel group: aspirin 100 mg + prasugrel 5 mg

PRU ≥220

- Clopidogrel group: aspirin 100 mg + clopidogrel 75 mg + cilostazol 100 mg
- Prasugrel group: aspirin 100 mg + prasugrel 5 mg + prasugrel 5 mg

The morning on the day of the procedure, after administering the drug at the adjusted dose, the planned intracerebrovascular procedure was performed.

7) Brain magnetic resonance imaging (MRI) was performed within 7 days from the day of the procedure (i.e., from the day of the procedure to 1 week after the procedure, and it varied depending on the clinical situation).
8) If there were no neurological abnormalities or complications, the patient was discharged with discharge medication on the next day following the procedure.
   - Clopidogrel group: aspirin 100 mg + clopidogrel 75 mg
   - Prasugrel group: aspirin 100 mg + prasugrel 5 mg

9) On postoperative day 30 (30-35 days after the procedure), the patient's clinical courses and complications were assessed. If there were no specific findings, the drug was changed to aspirin 100 mg + clopidogrel 75 mg in both groups.

- Time table

Procedure	Screening	Pre-medication	Admission	Medication adjustment	Treatment	Follow-up 1 (MR)	Follow-up 2	Follow-up 3
Time period	Day -60 ~ -6	Day -5 (out-patient)	Day -2 (in-patient)	Day -1 (in-patient)	Day 0 (in-patient)	Day 1 (in-patient)	Day 2 (discharge)	Day 30
Visit window	-	0~± 1 day	0~±1 day	0 ~+1 day	-	0~+1 day	0~+3 days	0~± 5 days
Informed consent	O	-						
Inclusion/Exclusion Criteria	O	-						
Demographic data	O	-	O					
Medical History	O	-	O					
Vital sign	O	-	O		O	O	O	O
Neurological examination	O	-	O		O	O	O	O
Aneurysm data	O	-						
Radiologic data	O	-			O	O		
Medication compliance	-	-	O					O
VerifyNow test	-	-	-	O				

Study Population

At the time of initial admission for pretreatment examination, patients were screened based on their medical history, vital sign evaluation, and laboratory tests (hematological tests, biochemical tests, urinalysis, and pregnancy test). Detailed inclusion and exclusion criteria of the present study were as follows:

- **Inclusion Criteria**

· Patients aged between 19 and 75 years

· Aneurysms without any evidence of rupture on an intracranial imaging study within the last 6 months

· Planned treatment with coil embolization with stent insertion or flow diverter insertion

· If the patient itself consented to this study

- **Exclusion Criteria**

· History of acute ischemic stroke or transient ischemic attack

· Any intracranial hemorrhage except subarachnoid hemorrhage due to aneurysm rupture within the last 3 months

· Concurrent treatment other than endovascular procedures (e.g., open craniotomy and microsurgical clipping)

· Contraindications to iodine contrast agents

· Already taking antiplatelet or antithrombotic drugs other than aspirin

· Hypersensitivity to aspirin, prasugrel, or clopidogrel

· Cardiac arrhythmia that should be needed to take anticoagulants

· Pregnant or lactating women

· Chronic kidney disease (GFR <60)

· Patients with chronic liver disease who had at least 100 IU/L of either AST/ALT in the liver function test

· Patients with pathological active bleeding, as seen in peptic ulcer

· Patients with genetic problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption because they contain lactose

· Patients continuously taking non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors

· Patients requiring concomitant administration of ≥15 mg methotrexate for a week

· If the case was difficult to follow up after treatment

Randomization

Randomization was conducted using the randomization program provided by the Seoul National University Hospital Biomedical Research Institute (http://mrcc.snu.ac.kr) and managed by a third party to ensure that the researchers were blinded to the assignments.

Study Endpoints

The primary endpoint was intraprocedural thromboembolic complications or

postprocedural ischemic stroke or death. The detailed information is as follows:

- A thromboembolism detected during the neurointerventional procedure
- Transient ischemic attack, ischemic stroke, or death with evidence of infarction on diffusion-weighted imaging, occurring within 30 days after the procedure

The secondary endpoints were postprocedural stroke and diffusion-restricted lesions on diffusion-weighted MRI. Another secondary endpoint was the preprocedural platelet function test value and its adjustment ratio. The details are as follows:

- Ischemic stroke in the relevant arterial territory within 30 days after the procedure
- Any stroke, including ischemic and hemorrhagic strokes, within 30 days after the procedure
- Disabling or fatal stroke within 30 days after the procedure
- Diffusion-restricted lesion detected on the 7-day postprocedural MRI

The safety endpoints were bleeding related to P2Y12 antagonists, including any bleeding within 30 days or major bleeding. Bleeding criteria followed the PLATelet inhibition and patient Outcomes bleeding criteria [4,5].

- Major bleeding criteria
  - ✓ Fatal bleeding (bleeding that directly results in death within 7 days)
  - ✓ Intracranial bleeding
  - ✓ Intrapericardial bleeding with cardiac tamponade
  - ✓ Hypovolemic shock or severe hypotension due to bleeding, requiring pressors or surgery
  - ✓ A decline in the hemoglobin level of ≥5.0 g/dL
  - ✓ Need for transfusion of at least 4 units of red blood cells

- Other major bleeding criteria
  - ✓ Bleeding that led to clinically significant disability
  - ✓ Decline in hemoglobin level of ≥3.0 g/dL but <5.0 g/dL
  - ✓ Need for transfusion of at least 2-3 units of red blood cells

- Minor bleeding criteria
  - ✓ Any bleeding requiring medical intervention but not meeting the criteria for major bleeding

Determination of the Sample Size

Given the hypothesis of the present study, we used a two-proportion Z-test with pooled variance and set the significance level at 0.05, power = 0.8.

In previous retrospective studies, intraprocedural thromboembolism occurred in the prasugrel group (0.009) and the clopidogrel group (0.064), with a -0.055 difference in the ratio of any stroke and death during the 30-day treatment. A total of 182 samples were required to prove significance at 80% for each group. Considering the 10% dropout rate, 203 patients were required per group, with a total of 406 patients.

Statistical Analysis

Statistical analysis was performed using SAS®(25) version 9.4 or later versions. All the efficacy analyses were based on the intention-to-treat principle. For comparison of all study endpoints (primary, secondary, and safety), 1) ratio data were analyzed using Pearson's chi-square test and 2) continuous variable comparison was analyzed using an independent two-sample t-test. All statistical tests were based on a two-tailed test with a significance level of 5%, and the safety analysis presented observations without correction for missing values.

- Baseline characteristics

Continuous variables are expressed as the mean ± standard deviation. Categorical and continuous variables of the baseline characteristics were compared and analyzed using the chi-square or Fisher's exact test and Student's t-test.

- All endpoints

For comparison of all endpoints (primary, secondary, and safety) in the two groups, 1) ratio-type data were analyzed using Pearson's chi-square test and 2) continuous variable comparison was analyzed using an independent two-sample t-test. Statistical significance was set at $P < 0.05$.

- Exploratory subgroup analyses

For the following pre-defined subgroups, subgroup analysis was performed to determine the difference between the overall primary and secondary endpoints.

- ✓ Previous major cardio-cerebrovascular accident
- ✓ Clopidogrel responsiveness (hyporesponder, PRU ≥220; responder, PRU<220)

- ✓ Cerebral aneurysm size in the stent group (<5 mm or ≥5 mm)
- ✓ Parent artery diameter (mean diameter <2.5 mm or ≥2.5 mm)
- ✓ Procedure (stent-assisted coiling, flow-diverter)
- ✓ Occlusion grade (Roy-Raymond classification)

The difference between the test and control groups according to subgroup followed the regression model with interaction.

Possible Risks and Benefits

Prasugrel and clopidogrel are widely used for treating cardiovascular diseases, and clopidogrel is the standard treatment for cerebrovascular diseases. In the case of prasugrel, a maintenance dose of 10 mg is used for patients with acute myocardial infarction, and a maintenance dose of 5 mg is used for those aged ≥75 years or those weighing <60 kg [6]. For participants in whom clopidogrel will be used, it will be beneficial to proceed with the established standard treatment; it has been reported that subjects using prasugrel have a lower level of drug resistance than the known resistance to the platelet action of clopidogrel due to the pharmacological mechanism. A higher drug effect is expected compared with clopidogrel.

Both clopidogrel and prasugrel may increase the risk of bleeding; however, this is the standard treatment guideline recommended for patients because the risk of treatment complications is not higher than that of the procedure. A retrospective study published in 2018 reported that low-dose prasugrel (5 mg) caused lower ischemic complications than 75 mg clopidogrel (0.9% vs. 6.4%, P = 0.011), and hemorrhagic complications were statistically significant. No significant difference was reported (0.5% vs. 2.2%, P = 0.218). Therefore, it cannot be concluded that the risk was particularly high in the prasugrel group in this study.

Definition of Adverse Events (AEs)

An AE is defined as any unintended or undesirable sign, symptom, or disease, regardless of whether it is associated with therapy or a drug. AEs will be evaluated from the time of providing informed consent and followed until resolution. An ongoing AE at the last visit will be followed up until the event is resolved or stabilized.

Serious AEs are defined as any event occurring during the study and are considered related to the study.

- ✓ Death
- ✓ Life-threatening condition

- ✓ Permanent or significant disability/incapacity/congenital anomalies/birth defects
- ✓ Result in hospital admission or prolonged hospital stay

In the event of unexpected or unpredictable AEs due to additional procedures and interventions, we considered the best possible treatment so that the study participants could receive appropriate medical treatment. If an adverse event occurs, it will be recorded in the adverse report form attached to the case record, and the principal investigator will report it to the Institutional Review Board Secretariat within 24 h of being recognized.

Potential Financial Risks

None

Conflict of Interest

None

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