Document for study participant

Date 2022.01.09

Subject title

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

1. Background

Unruptured intracranial aneurysm (UIA) is a relatively common disease with a prevalence of about 1% of the total population. However, it is one of the fatal hemorrhagic stroke and the mortality is exceeding 30% in overall case of subarachnoid hemorrhage. In the past decade, along with the development of neurointerventional therapy, there has also been a breakthrough in the treatment of UIAs. Widely accepted technique of neurointerventional therapy are coil embolization with or without stent deployment and flow diverter insertion. However, these two technique inevitably had the risk of thromboembolism. For the prevention and decrease, the dual antiplatelet therapy is commonly used in the clinical field.

Both aspirin and P2Y12 inhibitors, a dual antiplatelet drug combination therapy has been the regimen of choice for the patients with stent insertion in cardiologic and neurovascular field. 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 original role of platelet activity suppression in many situations, called “clopidogrel hyporesponse”. Low clopidogrel response has been reported in about 5-44% of the total population, which is associated with an increase in thromboembolism. However, there is no standard test method that can confirm this, and a standard value to define 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 response and platelet activity inhibition were compared before percutaneous coronary intervention (PCI) [1]. It has been reported that the platelet aggregation inhibitory effect is remarkably high. Representatively, according to Choi et al., the study 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 = .01), and the

bleeding risk was reported to be similar (0.5% vs 2.2%; P = .22) [2,3]. However, these recent studies are based on single-center retrospective data, so there is a limit to the level of evidence.

Your participation in this clinical study is at your discretion, and it does not affect the clinical judgment process for the treatment of this disease. Please take the time to read this explanation, and if you have any questions, please contact the researchers before deciding whether or not to participate.

2. Study drug

Drug name : plavix 75mg

Shape and characteristics : Pink round film-coated tablets

Dose : clopidogrel 75mg

Storage: tight container, room temperature storage (1~30℃)

Drug name : prasugrel 5mg

Shape and characteristics : Yellow Hexagonal Film Coated Tablets

Dose : prasugrel 5mg

Storage: tight container, room temperature storage (1~30℃)

3. Number of clinical trial participants and participation period

A total of 406 people participated in this study. The number of patients assigned to each participating institution's hospital is not set, and when a total of 406 patients are achieved through competitive recruitment from each institution, the study subject registration will be closed. If you decide to participate in this study, a hematological test will be performed to confirm the current patient's clinical condition.

The expected duration of this study is from January 2022 to July 2025.

4. Clinical trial method

The procedure you will receive from participation in this clinical study to termination are as follows:

① After a non-ruptured cerebral aneurysm is confirmed and admitted to the hospital, angiography is performed after clinical hematological tests such as blood tests and, if necessary, pregnancy tests. Fill out the consent form.

② The probability of being assigned to the test or control group by randomization using the randomization program is 50% to 50%, and it is assigned to the test group (Effient 5 mg + Aspirin 100 mg) and the control group (Plavix 75 mg + Aspirin 100 mg).

③ Starting from 5 days before the procedure, the drugs specified in the assigned group are taken once a day for 1 month, and an imaging test (MRI) is performed on the 1st month of the procedure, and the treatment effect of the drug, medication compliance and adverse reactions are checked. .

④ When the study is completed, patient management is continued based on the conventional method.

5. alternative treatment
If you decide not to participate in this study, your usual empirical treatment will apply and you can discuss this with your doctor. The usual treatment is to take Plavix, the same treatment as the control, and includes periodic brain magnetic resonance examinations.

6. Anticipated side effects, risks, and discomfort for study subjects

Effient drug in the test group included bleeding, thrombocytopenia, anemia, abnormal liver function, allergic reaction, angioedema, high blood pressure, hyperlipidemia, headache, back pain, dyspnea, nausea, dizziness, cough, atrial fibrillation, noncardiogenic chest pain, atrial fibrillation, Bradycardia, rash, fever, and diarrhea are known to occur. Plavix, the control drug, is associated with chest pain, fatigue, cold-like symptoms, edema, high blood pressure, headache, syncope, dizziness, abdominal pain, diarrhea, nausea, hyperlipidemia, arthralgia, purpura, upper respiratory infection, pruritus, urinary infection, bleeding disorder, neutropenia, It has been reported that agranulocytosis, indigestion, gastroenteritis, constipation, rash, nasal bleeding, depression, dyspnea, thrombotic thrombocytopenic purpura, etc. may occur.
However, this is not a complication reported by a large number, and it is not a drug that is reported to be dangerous for use in general patients because its safety is guaranteed. This study is a clinical trial to create high-quality evidence that has not yet been verified so that Effient, a drug that is widely and safely used for heart disease, can also be used in patients with cerebrovascular disease. In addition, the effient of the test group used in this study is a study consisting of about half the dose generally used for patients with cardiovascular disease, so the possibility and severity of side effects will be lower.
7. Factors to be observed by participant for research
In order to conduct accurate scientific research, please follow the continuous administration of the drug and other instructions of the attending physician. If you experience any discomfort during the study, please notify your attending physician without delay.

8. Expected benefits for participant
Details of the anticipated benefits to patients participating in this study are set out in Section 9. Pharmaceutically, there may or may not be benefits from administration. And the results obtained through this study can provide medical and economic help to other people who will be treated for the same disease in the future.

9. Compensation for expenses and damages
During the study period (from 5 days prior the procedure to 1 month after the procedure), the research director will pay the cost of the drug Effient and Plavix drug. If you meet the research subject selection criteria and agree to participate, you will receive a one-time payment of 50,000 won as a reward after filling out the consent form for research and treatment. However, the cost of general non-ruptured cerebral aneurysm treatment, platelet function tests, and radiology tests such as MRI are borne by the patient under the insurance regulations of the National Health Insurance Corporation. In addition, in case of side effects related to the prasugrel drug used in this study, the cost of testing and treatment, as well as compensation, are in accordance with the Victim Compensation Agreement.

10. Consent and withdrawal of consent to participate in research voluntarily
Participation in this study is voluntary, and even if you do not agree to participate, you will not be penalized for further treatment. You can freely stop participating in this study at any time

during the study period, and you will not receive any disadvantages for your next treatment. When it is decided to stop participating, the collected information such as case records that have been kept will be destroyed.

11. New information that may affect willingness to continue participating

We will notify you or your representative in a timely manner as new information becomes available that may affect your willingness to continue to participate in this study.

12. stop, drop out

① When a patient requests discontinuation of the study during the study period

② In case of clinical trial drug-related side effects

③ When the patient can no longer take the drug due to a change in the patient's disease or condition

④ In case of allergy to contrast medium or test drug

13. Information Collection, Use and Provision

By signing this consent form, you consent to the collection and use of your personal (sensitive) information by researchers.

1) Purpose of collection and use of personal information

The purpose of this study is to investigate the efficacy and safety of low-dose prasugrel versus clopidogrel in the treatment of stents or blood flow diverters for non-ruptured cerebral aneurysms through your personal (sensitive) information.

2) Items of personal (sensitive) information to be collected

1) Your name, gender, age, hospital registration number

2) Health-related information such as medical records and data generated during clinical research

3) Period of retention and use of personal information

Your personal (sensitive) information will be used for research for 3 years after the end of the research, and the collected personal information will be appropriately managed in accordance with the law.

4) You can freely decide whether to accept the collection, use, and provision of the above personal (sensitive) information. Even if you do not accept the collection, use, and provision of personal (sensitive) information, there will be no disadvantages in your treatment and prescription. The collected information is not provided to others.

14. Confidentiality of your identity

Records that identify you are confidential and not publicly available. However, within the scope permitted by relevant laws or regulations, your medical records or data may not be directly viewed by monitor agents, inspectors, review committees, and government agencies to verify the reliability of the research procedure and data. However, even in this case, we will try to keep it as confidential as possible. By signing this consent form, you are giving yourself direct access to these materials, and your identity will be kept confidential when the research results are published.

15. Provision of information on rights and interests as research subjects

You have the right to ask any questions about any known or possible risks associated with this research at any time.

If you have any questions about the rights and interests of the research subjects, you can contact the Research Review Board (IRB) of Yonsei University Yongin Severance Hospital (Tel: 031-5189-8891~2). And if you have any questions about this research, please contact Professor Chang Ki Jang (Tel: 031-5189-8484).

Informed Consent document

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

Clinical Research Director: Chang Ki Jang (Assistant Professor of Neurosurgery, Severance Hospital, Yongin)
Clinical research institute: Department of Neurosurgery, Yongin Severance Hospital, Yonsei University

I have read and understood all the information set prior to this clinical study and have received satisfactory answers to all my questions.····· □

I wish to participate in this clinical study voluntarily and understand that after consent I will be provided with a copy of the informed consent.····· ·· □

I agree to collect personal information such as name and address under strict confidentiality while participating in clinical research, and also agree to collect my medical records and clinical information.····· ····· ····· ··· □

Participant : _____ **Signature :** _____ **Date :** _____
legal representative : _____ **Signature :** _____ **Date:** _____
Relationship between participant and legar representative : _____

I confirm that I have explained in detail the purpose of this clinical study, test process, and risk factors to the above applicant.

Researcher Name: _____ **Signature:** _____ **Date:** _____