



Safety and Efficacy of Flow Diverter Therapy for Unruptured Intracranial Aneurysm Compared to Traditional Endovascular Strategy : A Multi-Center, Randomized, Open-Label Trial

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Objective : Endovascular treatment of large, wide-necked intracranial aneurysms by coil embolization is often complicated by low rates of complete occlusion and high rates of recurrence. A flow diverter device has been shown to be safe and effective for the treatment of not only large and giant unruptured aneurysms, but small and medium aneurysms. However, in Korea, its use has only recently been approved for aneurysms <10 mm. This study aims to compare the safety and efficacy of flow diversion and coil embolization for the treatment of unruptured aneurysms ≥ 7 mm.

Methods : The participants will include patients aged between 19 and 75 years to be treated for unruptured cerebral aneurysms ≥ 7 mm for the first time or for recurrent aneurysms after initial endovascular coil embolization. Participants assigned to a flow diversion cohort will be treated using any of the following devices : Pipeline Flex Embolization Device with Shield Technology (Medtronic, Minneapolis, MN, USA), Surpass Evolve (Stryker Neurovascular, Fremont, CA, USA), and FRED or FRED Jr. (MicroVention, Tustin, CA, USA). Participants assigned to a coil embolization cohort will undergo traditional endovascular coiling. The primary endpoint will be complete occlusion confirmed by cerebral angiography at 12 months after treatment. Secondary safety outcomes will evaluate periprocedural and post-procedural complications for up to 12 months.

Results : The trial will begin enrollment in 2022, and clinical data will be available after enrollment and follow-up.

Conclusion : This article describes the aim and design of a multi-center, randomized, open-label trial to compare the safety and efficacy of flow diversion versus traditional endovascular treatment for unruptured cerebral aneurysms ≥ 7 mm.

Key Words : Aneurysm · Embolotherapy · Endovascular procedures · Prospective studies · Flow diverter.

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INTRODUCTION

The prevalence of intracranial aneurysms is 0.4–3.0%^{25,28}, and aneurysmal rupture results in subarachnoid hemorrhage that has a decimal prognosis with substantial mortality and morbidity^{4,28,29}. Advances in non-invasive brain imaging methods such as magnetic resonance angiography have facilitated the diagnosis of unruptured intracranial aneurysms²⁴, and the preventive treatment of unruptured intracranial aneurysm is generally recommended for an aneurysm with a diameter ≥ 7 mm²⁵.

Microsurgical clipping and endovascular coil embolization are two major treatment modalities for intracranial aneurysms⁵. Equipped with the advantage of non-invasiveness and advances in devices and techniques, coil embolization has become the dominant treatment choice with lower procedural morbidity and mortality^{3,12,18}. However, coil embolization of wide-necked aneurysms is still difficult; even with adjunct use of stent, recurrence and retreatment rates are approximately 12% and 6%, respectively^{7,15}. Furthermore, larger aneurysms are associated with higher rates of recurrence even when complete or near-complete occlusion has been initially achieved, due to coil compaction leading to recanalization^{10,11,17}. A study revealed that large aneurysms (≥ 7 mm) were more likely to recur than smaller aneurysms (< 7 mm) after coil embolization²⁶.

Flow diversion has been developed to address the challenges faced during traditional coil embolization. Flow diverters are designed to exert lower radial force to improve conformability and provide increased metal surface coverage for improved flow diversion, compared to conventional intracranial stents²⁷. They elicit remodeling of the parent artery primarily through the following mechanisms: 1) exclusion of blood flow into the aneurysmal sac, resulting in thrombus formation inside the sac and 2) provision of a scaffold for endothelialization²³. A clinical trial using the Pipeline embolization device (Medtronic, Minneapolis, MN, USA), the first commercially available flow diverter, revealed that flow diversion of large aneurysms (> 10 mm) in the internal carotid artery with wide neck (> 4 mm) showed a complete occlusion rate of 86% at 12 months, and major morbidity and mortality rate of 5.6%¹, and the device was approved by the United States Food and Drug Administration (FDA) for use in large aneurysms (> 10 mm) with wide neck (> 4 mm). Subsequently, a recent clinical trial using the

Pipeline Flex embolization device for unruptured wide-necked aneurysms ≤ 12 mm demonstrated complete occlusion rate of 76.8% at 12 months with a major morbidity and mortality rate of 2.1%¹³. The U.S. FDA has expanded the instructions for its use in wide-necked aneurysms with a small- and medium-sized aneurysms.

In Korea, the flow diverter was initially approved for use in the treatment of unruptured aneurysms ≥ 15 mm, and only recently was it approved for aneurysms ≥ 10 mm. Currently, endovascular treatment options for wide-necked aneurysms < 10 mm are limited to traditional procedures such as parent artery occlusion, coil embolization by multiple-catheter technique, or balloon or stent-assist technique.

The aim of this study is to assess the safety and efficacy of flow diversion treatment of unruptured intracranial aneurysms ≥ 7 mm by evaluating complication rates and complete occlusion rates at 12 months compared to traditional endovascular treatment in patients who are either to receive the first treatment or retreatments for recurrent aneurysms after initial endovascular treatment.

MATERIALS AND METHODS

Design

This is a prospective, multicenter (13 institutions), randomized, open-label trial to compare the safety and efficacy of treatment of unruptured cerebral aneurysms or recurrent cerebral aneurysms with a maximum diameter ≥ 7 mm by flow diversion versus coil embolization with or without adjunctive balloon or stent devices. Approval of the institutional review board at each participating institution has been obtained (see Supplementary Data 1). Participants will be randomly assigned to flow diversion or traditional endovascular treatment cohorts in a 1 : 1 fashion. The primary endpoint will be complete occlusion confirmed by catheter cerebral angiography at 12 months after endovascular treatment.

Study population

The study population will include patients aged between 19 and 75 years diagnosed with unruptured intracranial aneurysms or with recurrent aneurysms after initial endovascular treatments with a maximum diameter ≥ 7 mm arising from the internal carotid artery, anterior cerebral artery, middle ce-

rebral artery, or vertebrobasilar arteries. Recurrent aneurysms are defined as grade 2 (70% to 89% aneurysm occlusion in orthogonal images of catheter cerebral angiography from optimal projection) or higher according to the aneurysm occlusion grading system for endovascular aneurysm occlusion suggested by Meyers et al.¹⁶⁾ (Table 1). Detailed inclusion and exclusion criteria of the study are described in Table 2.

Informed consent

The informed consent form will contain extensive information about this trial including the purpose of the trial, the study design, potential risks and benefits associated with the trial, and the participants’ rights and responsibilities.

Randomization

After complete explanation of the trial and signing informed consent, participants will be enrolled to the trial and

randomized to either the flow diversion or coil embolization cohort in a 1 : 1 ratio using a computer-generated randomized sequence. For allocation concealment, central randomization will be performed, and a random number table will be kept by a third party other than the investigators. The participant will be informed of the treatment he/she is assigned when signing the informed consent for the treatment.

Treatment

Patients assigned to flow diversion will undergo placement of any of the following flow diverters available in Korea : Pipeline Flex Embolization Device with Shield Technology (Medtronic), Surpass Evolve (Stryker Neurovascular, Fremont, CA, USA), and FRED or FRED Jr. (MicroVention, Tustin, CA, USA). Participants assigned to coil embolization will undergo endovascular coiling of aneurysms with or without adjunctive balloon or stent devices. Dual antiplatelet agents comprising of aspirin 100 mg and clopidogrel 75 mg will be administered to all participants 5 to 7 days prior to the procedure and continued for a maximum of 12 months, after which aspirin monotherapy will be maintained for at least 2 years after the procedure.

Clinical and radiologic outcome measures

The primary endpoint will be complete occlusion (grade 0 or 1 confirmed by catheter cerebral angiography according to the Aneurysm occlusion grading system) at 12 months after the treatment. Secondary endpoints will evaluate the short-

Table 1. Aneurysm occlusion grading system

Grade	Definition
0	Complete aneurysm occlusion
1	90% or greater aneurysm occlusion
2	70–89% aneurysm occlusion
3	50–69% aneurysm occlusion
4	25–49% aneurysm occlusion
5	Less than 25% aneurysm occlusion

Reproduced from the original article by Meyers et al.¹⁶⁾

Table 2. Inclusion and exclusion criteria of the study

	Criteria
Inclusion	<ol style="list-style-type: none"> 1. Agreement of the patient for participation in the study and informed consent signed by the patient 2. Age between 19 and 75 years 3. Unruptured intracranial aneurysm with the maximum diameter ≥7 mm <ul style="list-style-type: none"> - First treatment or - Treatment for recurrent aneurysm after initial endovascular treatment, confirmed as aneurysm occlusion grading system grade 2 or above
Exclusion	<ol style="list-style-type: none"> 1. Participants with severe neurologic deficit (modified Rankin scale score ≥3) 2. Participants at a high risk of thromboembolic cerebral infarction 3. Participants with other intracranial pathologies such as brain tumor, Moyamoya disease, arteriovenous malformations, etc.) 4. Participants contraindicated for endovascular procedures due to unfavorable vascular anatomy or contraindication to antiplatelet therapy 5. Participants with poor medication compliance 6. Participants with severe hepatic failure or renal failure (eGFR <30 mL/min/1.7 m²) 7. Participants with psychiatric disorders

eGFR, estimated glomerular filtration rate

term and the longer-term safety of the trial, and include the following : 1) any procedure-related complications defined as thromboembolic or hemorrhagic complications that occur within 30 days after the treatment, 2) severity of hemorrhage evaluated by Thrombolysis in Myocardial Infarction bleeding criteria⁸⁾, 3) delayed intracranial hemorrhage defined as spontaneous intracranial hemorrhage that occurs within 12 months after treatment, 4) delayed cerebral infarction defined as cerebral infarction due to thromboembolism within 12 months after treatment, and 5) neurologic status evaluated using the modified Rankin scale score at 1 month and 12 months. A summary of the scheduled visits is shown in Table 3.

Sample size

The primary endpoint will be the complete occlusion of the aneurysm at 12 months after the endovascular treatment. Based on data from previous studies, we estimate the long-term complete occlusion rate of cerebral aneurysms ≥ 7 mm to be 80%^{9,14,19)}. The complete occlusion rate of recurrent aneurysms treated with flow diversion was 94.1%²⁰⁾, and considering the improvements in device and technique, we estimate the complete occlusion rate of cerebral aneurysms using flow diverters to be 95%, yielding a risk difference of 15%. Taking into account a significance level of 0.05, and power of 80% for

the two-sided chi-square test, the number of participants required is 76 per group. Based on our previous experience in which drop-outs of cerebral aneurysm patients were relatively rare, we expect a patient dropout rate of 5%, yielding the total number of patients required for the study to be 160 (80 patients per group).

Statistical analysis

The principal method of analysis is intention-to-treat analysis and a full analysis set will be used for statistical analysis, but per-protocol analysis may also be performed, as flow diverters may not be feasible in cases with unfavorable complex vascular anatomy. For bivariate analysis, a two-sample t-test or Mann-Whitney U test will be performed for continuous variables, and the chi-square test or Fisher's exact test will be used for categorical variables. The primary and secondary outcomes will be evaluated by logistic regression analysis, and the effect size will be presented as odds ratios and 95% confidence intervals.

RESULTS

The trial will begin enrollment in 2022, and clinical data

Table 3. Study visits

Visit	V0*	V1*	V2	V3
Time in relation to the intervention	Within 4 weeks prior to V1	Day 0	Month 1 \pm 2 weeks	Month 12 \pm 4 weeks
Informed consent	●			
Collection of demographic information	●			
Past medical history/family history	●			
Vital signs	●	●	●	●
Electrocardiogram	●			
Laboratory tests	●			●
Pregnancy test	●			
Inclusion/exclusion criteria confirmation	●			
Randomization [†]	●	●		
Endovascular treatment	●	●		
Radiologic evaluation [‡]	●			●
Adverse event	●	●	●	●
Concomitant drug check	●	●	●	●

*V0 and V1 can coincide if a participant meets the inclusion/exclusion criteria. [†]Randomization of eligible participants may occur at any time between V0 and V1. [‡]Radiologic evaluation must include catheter cerebral angiography and additional angiography (e.g., computed tomography angiography or magnetic resonance angiography) may be performed

will be available after enrollment and follow-up.

DISCUSSION

This study aims to provide definitive data on the safety and efficacy of flow diversion with devices available in Korea in comparison to traditional endovascular treatment for unruptured cerebral aneurysms ≥ 7 mm.

Previously, several studies have compared the treatment outcomes of flow diversion and coil embolization, but they were retrospective studies. A systematic review and meta-analysis by Zhou et al.³²⁾ reported that flow diversion showed a significantly higher complete occlusion rate than coil embolization and a subgroup of stent-assisted coil embolization. A recent meta-analysis comparing flow diversion treatment with conventional endovascular treatment revealed that flow diversion was associated with higher 6-month complete occlusion rate for large or giant aneurysms, but no such difference was observed for non-large or giant aneurysms³⁰⁾. The current randomized trial is expected to minimize selection bias and confounding factors due to unequal distribution of significant factors, and to warrant direct comparison of the two treatment methods.

The off-label use of flow diverters for aneurysms < 10 mm has already been prevalent, and its efficacy and safety have also been reported for different flow diverters such as FRED (MicroVention)^{2,21)} and SILK (Balt Extrusion, Montmorency, France)²²⁾. A meta-analysis of flow diversion treatment for intracranial aneurysms < 10 mm revealed the complete occlusion rate of 84.2%, and procedure-related mortality and morbidity of 0.9% and 5.2%, respectively³¹⁾. A matched-cohort study by Chalouhi et al.⁶⁾ demonstrated that flow diversion was associated with a significantly higher complete occlusion rate than coil embolization (70% and 47.5%, respectively, $p=0.04$) without additional morbidity in the treatment of small aneurysms < 10 mm. To date, no study has directly compared the treatment outcomes of flow diversion and traditional endovascular coiling for treatment of aneurysms < 10 mm.

CONCLUSION

This article describes the design of a multi-center, random-

ized, open-label trial to compare the safety and efficacy of the treatment of unruptured cerebral aneurysms with maximum diameter ≥ 7 mm by flow diversion versus traditional endovascular treatment. This trial is expected to warrant direct comparison of the two treatment methods with minimal bias.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : JK, GH, BTK, SQP, JSO, SPB, OKK, JC, Committee of Multicenter Research, Korean Neuroendovascular Society; Funding acquisition : OKK, JC; Methodology : JK, GH, BTK, SQP, JSO, SPB, OKK, JC, Committee of Multicenter Research, Korean Neuroendovascular Society; Project administration : JK, GH, BTK, SQP, JSO, SPB, OKK, JC, Committee of Multicenter Research, Korean Neuroendovascular Society; Writing - original draft : JK; Writing - review & editing : OKK, JC

Data sharing

None

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• Supplementary materials

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