

Risk Factors for Periprocedural Ischemic Stroke following Endovascular Treatment of Intracranial Aneurysms

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Research

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Abstract

Background

The aim of this study was to comprehensively evaluate the risk factors of periprocedural ischemic stroke associated with endovascular treatment of intracranial aneurysms using a real-world prospective database.

Methods

From August 2016 to March 2017, 200 patients with 217 aneurysms who underwent 206 endovascular procedures were enrolled. Univariate analysis and multivariate logistic regression analysis were used to examine the risk factors for periprocedural ischemic stroke.

Results

Among the 206 endovascular procedures, periprocedural ischemic stroke occurred in 23 procedures (11.17%). After univariate analysis, the ischemic group had a higher proportion of large (≥ 10 mm) aneurysms than the control group (39.1% vs. 20.2%, $p = 0.040$). The incidence of periprocedural ischemic stroke was higher in cases treated by flow diverter (18.60%) or stent-assisted coiling (12.28%) than in cases treated by coiling only (2.04%), and the differences were statistically significant ($p = 0.036$). After multivariate logistic regression analysis, treatment modality was the independent risk factor for periprocedural ischemic stroke. Compared with the coiling-only procedure, flow diverter therapy was associated with a significantly higher rate of periprocedural ischemic stroke (OR 13.839; 95% CI 1.617–118.416; $p = 0.016$). Stent-assisted coiling also tended to present more often with periprocedural ischemic stroke than coiling alone (OR 7.559; 95% CI 0.958–59.618; $p = 0.055$).

Conclusions

Aneurysm size and treatment modality were associated with periprocedural ischemic stroke. Larger aneurysms were associated with increased risk of periprocedural ischemic stroke. Flow diverter therapy was associated with significantly more periprocedural ischemic stroke than the coiling procedure alone.

Introduction

In recent decades, endovascular treatment has become a major modality in the treatment of intracranial aneurysms, because the safety and efficacy have been demonstrated in numerous large clinical studies[1–3]. With the endovascular device improvements and increasing clinical experience, intracranial aneurysms could be treated by a more rational modality according to patient or aneurysm characteristics, which increased the aneurysm occlusion rates[4]. For instance, the wide-neck aneurysms (≥ 4 mm or dome-neck ratio ≤ 2) was usually treated by intracranial stent [5]. But for large or complex aneurysms, flow diverter therapy is the preferred treatment[6, 7].

However, endovascular treatment of intracranial aneurysm has the risk of neurological complications. Periprocedural ischemic stroke is the most common neurologic complication following endovascular treatment of intracranial aneurysms, and is a major source of neurological morbidity and mortality[8, 9]. A better understanding of the risk factors for periprocedural ischemic stroke is important, and may prove beneficial in the decision-making process of intracranial aneurysm management. However, limited studies have comprehensively evaluated the risks of periprocedural ischemic stroke associated with endovascular treatment of intracranial aneurysm using a real-world prospective database. Therefore, the aim of this study was to evaluate the incidence and risk factors of periprocedural ischemic stroke following endovascular treatment using a prospective database. The clinical, aneurysmal and procedural characteristics associated with periprocedural ischemic stroke were analyzed in this study.

Materials And Methods

Patient selection

This study is a subanalysis of a prospective study (the HARET study)[10]. The inclusion and exclusion criteria for the HARET study have been published previously. Briefly, patients with intracranial saccular aneurysms who underwent endovascular treatment in our institute between August 2016 and March 2017 were enrolled in the HARET study. The exclusion criteria included intracranial aneurysm with previous treatment, treatment by parent vessel occlusion, treatment by a covered stent, presence of a brain arteriovenous malformation and presence of a dissecting aneurysm. Two hundred eligible patients (217 aneurysms) were enrolled in this prospective study. The study was approved by our institutional review board. All patients or their relatives provided written informed consent during hospitalization. This subgroup analysis of the HARET study examined the variables associated with periprocedural ischemic stroke. Clinical, aneurysmal and procedural factors were recorded and analyzed. These factors were as follows: age, sex, history of alcohol intake and cigarette smoking, hypertension, hyperlipidemia, previous ischemic comorbidity, aneurysm size (maximum size), shape (irregular: blebs, nipples or multiple lobes), sidewall/bifurcation, location (anterior/posterior circulation), distal aneurysm (at or distal to the Circle of Willis), whether the aneurysm was ruptured or unruptured, and treatment modalities (including coiling only, stent-assisted coiling or flow diverter treatment). The occurrence of periprocedural ischemic stroke within 30 d of the endovascular treatment was also recorded, and the 200 eligible patients were divided into two groups (ischemic group and control group). All patients and aneurysms with periprocedural ischemic complications were included in the ischemic group. A major ischemic event was defined as an event lasting for more than 7 d, and a minor ischemic event was defined as an event that resolved within 7 d with no clinical sequelae[11]. All major ischemic events were included in the neurologic morbidity and mortality rates.

Endovascular procedures

For each endovascular procedure, the treatment strategy was discussed and chosen at the weekly peer-reviewed endovascular conference. Coiling alone was performed if the aneurysm neck was narrow (< 4

mm or dome-neck ratio > 2). For wide-neck aneurysms (≥ 4 mm or dome-neck ratio ≤ 2), the stent-assisted coiling technique was used. However, if the aneurysm was large or complex and therefore unsuitable for conventional endovascular treatment (coiling or stent-assisted coiling), the aneurysm was treated by a flow diverter. Endovascular treatment was performed under general anesthesia and systemic intravenous heparin. If stent-assisted coiling or flow diverter therapy was chosen, 100 mg/d aspirin and 75 mg/d clopidogrel were administered for at least 5 d before the procedure for unruptured aneurysms, and a loading dose (300 mg) of aspirin and clopidogrel was given before the procedure for ruptured aneurysms. Patients were treated with coiling, stent-assisted coiling or flow diverter therapy as appropriate. After the procedure, patients treated with the conventional stent were given 75 mg/d clopidogrel for 6 wk and 100 mg/d aspirin for 6 m, while patients treated with the flow diverter were given 75 mg/d clopidogrel for 3 m and 100 mg/d aspirin thereafter.

Statistical Analysis

Data are presented as the mean \pm standard deviation for quantitative variables and frequency for qualitative variables. Risk factors associated with periprocedural ischemic complications were analyzed using an independent sample t-test, or a χ^2 test applied as appropriate. Then, variables with $p < 0.20$ in the univariate logistic analysis were included in the multivariate logistic regression. Statistical significance was considered as $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, v.22.0 (IBM Corp., Armonk, NY, USA). All statistical analyses were performed on a per-procedure basis. Some endovascular procedures were used to treat more than one aneurysm within a single patient, in which case the first aneurysm for each procedure was used in the analysis[11].

Results

Clinical and aneurysmal characteristics

In total, from August 2016 to March 2017, 200 patients with 217 aneurysms were included in this study. The patients consisted of 128 females and 72 males. The mean age of the patients was 56.05 ± 10.34 years. Among the 217 aneurysms, 186 cases (85.71%) were unruptured and 31 cases (14.29%) were ruptured. The mean size of the aneurysms was 7.46 ± 5.08 mm. Of the 217 aneurysms, 54 aneurysms were treated with coiling alone, 116 aneurysms with stent-assisted coiling and 47 aneurysms with flow diverter therapy.

Periprocedural ischemic stroke

In the current study, 206 endovascular procedures were performed for the 217 aneurysms. Among the 206 endovascular procedures, periprocedural ischemic stroke occurred in 23 procedures (11.17%). The 23 periprocedural ischemic strokes consisted of two intraprocedural thrombus formations, eight minor ischemic complications and 13 major ischemic complications. Among the 23 periprocedural ischemic strokes, eight cases presented with transient neurologic symptoms that resolved on discharge and 15 cases showed persistent neurologic morbidity (7.28%). No mortality was observed.

Risk factors for periprocedural ischemic stroke

As shown in Table 1, after univariate analysis, aneurysm size was significantly correlated with occurrence of periprocedural ischemic stroke. The ischemic group had a higher proportion of large aneurysms (≥ 10 mm) than the control group (39.1% vs. 20.2%, $p = 0.040$). Moreover, the incidence of periprocedural ischemic stroke was higher in cases treated by flow diverter therapy (18.60%) or stent-assisted coiling (12.28%) than in cases treated by coiling only (2.04%), and the difference was statistically significant ($p = 0.036$) (figure 1). The other clinical and aneurysmal factors examined (age, sex, smoking, drinking, hypertension, hyperlipidemia, previous ischemic stroke, rupture status, shape, location, sidewall/bifurcation and distal/proximal to the circle of Willis) showed no significant differences between the ischemic and control groups ($p \geq 0.05$).

Multivariate logistic regression analysis

The multivariate logistic regression results are presented in Table 2. After multivariate logistic regression analysis, treatment modality was found to be the only independent risk factor for periprocedural ischemic stroke. Compared with the coiling-only procedure, flow diverter therapy was associated with a significantly higher rate of periprocedural ischemic stroke (OR 13.839; 95% CI 1.617–118.416; $p = 0.016$). Stent-assisted coiling also tended to present with a higher rate of periprocedural ischemic stroke than coiling alone (OR 7.559; 95% CI 0.958–59.618; $p = 0.055$).

Discussion

Periprocedural ischemic stroke is a major complication of endovascular treatment and is a major cause of neurologic morbidity or even mortality. In the current study, using a real-world prospective database, we comprehensively evaluated potential risk factors associated with periprocedural ischemic stroke after endovascular treatment of intracranial aneurysm. A main finding is that aneurysm size and endovascular treatment modality were associated with the occurrence of periprocedural ischemic stroke. Treatment modality was the only independent risk factor for periprocedural ischemic stroke in this study. We believe the results of this study could provide a beneficial reference for physicians.

Larger aneurysms are associated with increased risk of periprocedural ischemic stroke[12]. Intra-aneurysmal clot is more frequent in larger aneurysms before endovascular treatment, and larger aneurysms are more likely to have residual flow within the coil mass than small aneurysms[13-15]. Furthermore, for stent deployment, large size aneurysms can make it difficult to achieve good wall apposition, thus increasing the risk of periprocedural ischemic stroke[8]. The present study also found that the ischemic group had a higher proportion of large aneurysms than the control group.

Treatment modality was also associated with periprocedural ischemic stroke after endovascular treatment. Compared with coiling treatment alone, the risk of ischemic events is particularly high after stent-assisted coiling or flow diverter deployment, which may be due to the thrombogenicity of intra-arterial devices, longer procedure times and the complexity of the procedures[16]. Moreover, the disturbed

flow across the aneurysm neck with ingress and egress through the stent lumen may also increase the risk of periprocedural ischemic stroke[17]. In this study, treatment modality was the only independent risk factor for periprocedural ischemic stroke.

Periprocedural ischemic stroke mainly results from embolic events during endovascular treatment of intracranial aneurysms, such as the stent wall thrombus, original thrombus, or fresh clot migrating distally during the procedure[18]. Because platelets are the primary component of thrombi, inhibition of platelet reactivity can reduce the occurrence of ischemic complications, especially for stent deployment therapy[14]. Therefore, dual antiplatelet therapy (aspirin and clopidogrel) is widely accepted as the standard protocol to decrease the risk of ischemic complications for intracranial aneurysms treated with stents[17]. However, many patients still suffer periprocedural ischemic stroke after stent deployment, even though the standard antiplatelet medication protocol is applied[18]. Therefore, individualized antiplatelet therapy still needs to be investigated.

There are several limitations of our study. First, a limited number of cases were included from a single center, which may limit the generalization of the results. Also, computerized tomography and magnetic resonance are not part of the routine clinical examination after endovascular treatment, so some asymptomatic ischemic complications may not have been detected. Finally, long-term follow-up results were not included in the study; these will be reported in future work.

Conclusion

Ischemic stroke was the most common procedure-related complication of endovascular treatment. Larger aneurysms increased the risk of periprocedural ischemic stroke. Treatment modality was the only independent risk factor of periprocedural ischemic stroke found in this study. Flow diverter therapy resulted in significantly more periprocedural ischemic stroke than the coiling procedure alone.

Abbreviations

HARET: Haemodynamic analysis for recanalisation of intracranial aneurysms after endovascular treatment

OR: odd ratio

CI: confidence interval

Declarations

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Not applicable.

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Data availability statement

In addition to the data published within this article, anonymized data can be obtained by request by any qualified investigator.

Consent for publication

Not applicable.

Competing Interests Statement:

We declare that we have no conflict of interest.

Contributorship Statement:

Yisen Zhang performed the statistical analysis and the manuscript writing. Chao Wang, Zhongbin Tian, Wei Zhu, and Wenqiang Li acquired the data. Xinjian Yang and Jian Liu analyzed and interpreted the data. Ying Zhang and Jian Liu conceived and designed the research, and handled funding and supervision.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Results from univariate statistical analysis for all variables on a per-procedure basis.

| Characteristics | Control group (N=183) | Ischemic group (N=23) | P value |
|----------------------------------|-----------------------|-----------------------|---------|
| Age(y) | 55.57±10.24 | 58.17±12.01 | 0.261 |
| Sex(%) | | | 0.864 |
| Male | 67(36.6) | 8(34.8) | |
| Female | 116(63.4) | 15(65.2) | |
| Smoking(%) | 29(15.8) | 4(17.4) | 0.999 |
| Drinking(%) | 24(13.1) | 2(8.7) | 0.788 |
| Hypertension (%) | 93(50.8) | 15(65.2) | 0.193 |
| Hyperlipidemia | 51(27.9) | 6(26.1) | 0.857 |
| Previous ischemic stroke | 28(15.3) | 4(17.4) | 0.999 |
| Aneurysm size | | | 0.040 |
| <10 mm | 146(79.8) | 14(60.9) | |
| ≥ 10 mm | 37(20.2) | 9(39.1) | |
| Rupture(%) | 28(15.3) | 1(4.3) | 0.269 |
| Shape(%) | | | 0.709 |
| regular | 112(61.2) | 15(65.2) | |
| irregular | 71(38.8) | 8(34.8) | |
| Location(%) | | | 0.243 |
| Anterior circulation | 169(92.3) | 19(82.6) | |
| Posterior circulation | 14(7.7) | 4(17.4) | |
| Sidewall/bifurcation aneurysm(%) | | | 0.591 |
| Sidewall | 114(62.3) | 13(56.5) | |
| Bifurcation | 69(37.7) | 10(43.5) | |
| Distal aneurysm | 55(30.1) | 9(39.1) | 0.375 |
| Treatment therapy (%) | | | 0.036 |
| coiling | 48(26.2) | 1(4.3) | |
| Stent-assisted coiling | 100(54.6) | 14(60.9) | |
| flow diverter | 35(19.1) | 8(34.8) | |

Table 2 Multivariate logistic regression results

| Variables | OR, 95% CI | p value |
|------------------------|------------------------|---------|
| Hypertension | 2.31(0.908, 5.887) | 0.079 |
| Aneurysm size | | |
| ≤10 mm | | Ref |
| ≥ 10 mm | 1.042(0.964, 1.127) | 0.211 |
| Treatment Therapy | | |
| Coiling | | Ref. |
| Stent assisted coiling | 7.559(0.958, 59.618) | 0.055 |
| Flow diverter | 13.839(1.617, 118.416) | 0.016 |

Figures

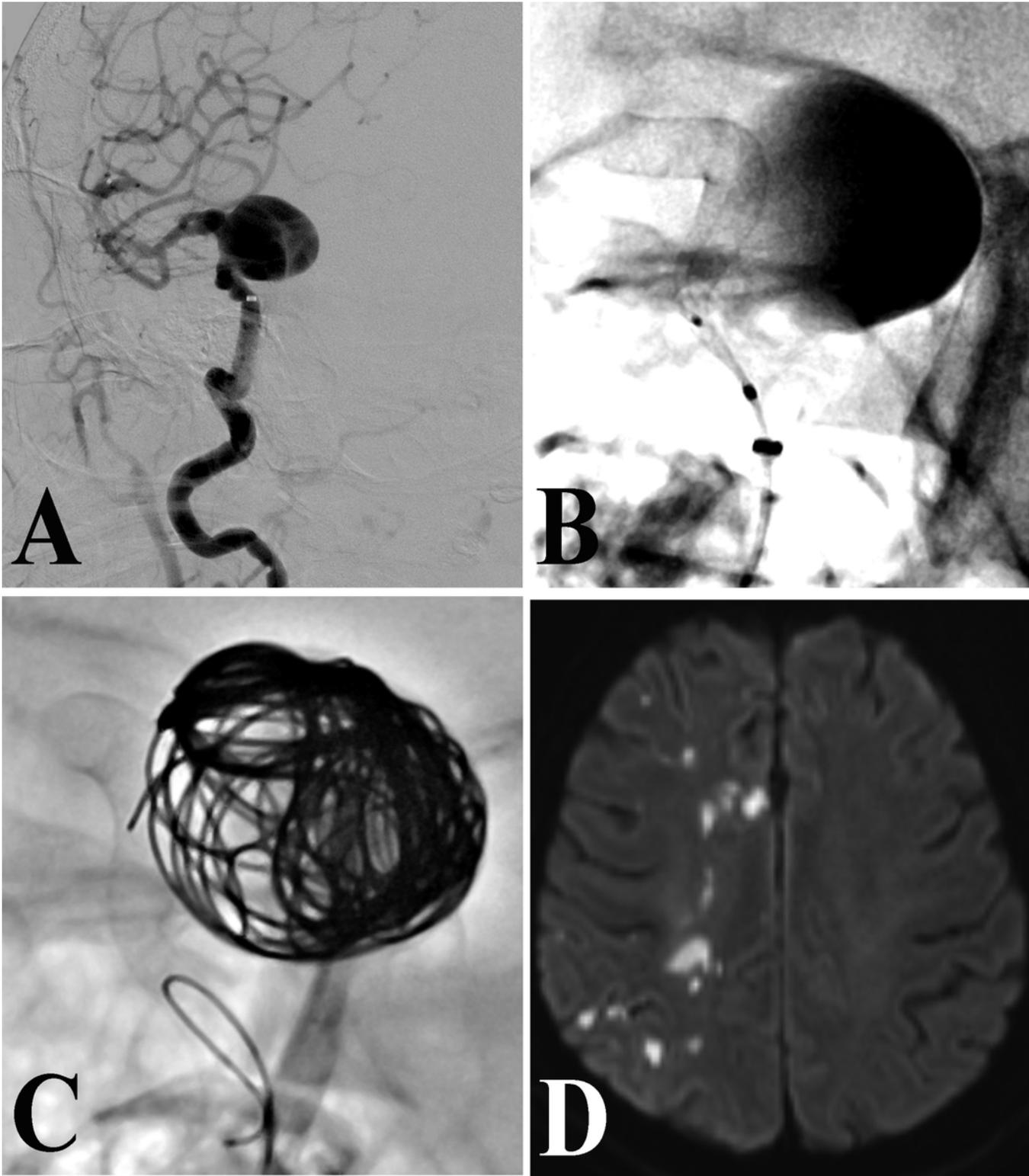


Figure 1

A patient with a large aneurysm was treated by flow diverter with loose packing. (A) Digital subtraction angiogram showed the large aneurysm. (B) The pipeline embolization device was deployed. (C) Loose coils package was formed in the aneurysm sac. Five hours after the endovascular procedure, the patient presented with the weakness of the right limb. (D) Magnetic resonance imaging showed the infarct lesion.