A comprehensive review of intracranial aneurysm and comparison between different treatment to the disease

Ningquan Zhang^{1*}

¹Shanghai Pinghe school, Shanghai, 200000, China

Abstract. An intracranial aneurysm is an abnormal protrude in the intracranial arteries' wall, which is the primary cause of hemorrhagic arachnoid. It is the third cerebrovascular disease besides cerebral thrombosis and hypertensive cerebral hemorrhage. There are many methods of treating intracranial aneurysms. Different methods have different outcomes and have their own advantages and drawbacks. This review provides comprehensive information on intracranial aneurysms and focuses on the comparison of different clinical methods treating this disease. Given the significant health concern of intracranial aneurysms, more attention should be paid, and innovative treating methods would be reasonably expected.

1 Introduction

1.1 Associated disorder

The most well-known inherited disorder related to the intracranial saccular aneurysm is Autosomal dominant polycystic kidney disease [1-4]. Multiple endocrine neoplasia type I [5], hereditary hemorrhagic telangiectasia [6], Ehlers-Danlos syndrome type IV [7], Marfan's syndrome [8], and neurofibromatosis type I [9] are also related diseases of intracranial aneurysm. The increasing occurrence of aneurysms in the brain has also been associated with moyamoya disease [10], intracranial arteriovenous malformations [11], sickle-cell disease [12], systemic lupus erythematosus [13], fibromuscular dysplasia [14], and coarctation of the aorta [15].

1.2 Location of the aneurysm

The aneurysms can locate in different sites over the whole body. The internal carotid artery, the anterior communicating artery to anterior cerebral artery junction, the middle cerebral artery branch points, the ophthalmic artery origin, and the internal carotid artery bifurcation are the frequently occurred sites of intracranial aneurysm. In the vertebrobasilar distribution, the tip of the basilar artery, the superior cerebellar artery branch from the basilar artery, the anterior inferior cerebellar artery branch from the basilar artery, and the posterior inferior cerebellar artery branch from the vertebral artery are the most common sites.

The patients that have ruptured intracranial aneurysms are likely to have multi-onset of aneurysms [16]. Some patients, about 20%, will have more than one aneurysm lesion [17].

1.3 Risk factors

The commonly applied risk factors in aneurysm related disease detection are summarized below as:

- Untreatable factors: sex, old age, and genetic factors.
- Treatable factors: smoking [18, 19], heavy alcohol use [18, 20, 21], hypertension [19, 20, 22] and drug use including cocaine and high dose of estrogen [23-25].
- Associated factors: low BMI (still not very clear) [26].

2 Epidemiology of aneurysm

2.1 Distribution of intracranial aneurysm.

2.1.1 Distribution in regions and countries.

Intracranial saccular aneurysms are also called berry aneurysms because their special appearance is one of the intracranial aneurysms, and they are like to occur in 1–2% of the population [27, 28] and cause about 80–85% of non-traumatic subarachnoid hemorrhages [29].

The overall occurrence of intracranial saccular aneurysms in human bodies is about 3.2% [30]. It is suggested that the prevalence of intracranial saccular aneurysms in the whole population is about 0.5–3%, from the findings of some imaging devices like arteriography and MRI [31, 32]. About 1.8% of adult participants have an aneurysm detected by screening MRI in European countries [33]. In a typical study of the Chinese population [34], 7% of middle-aged to old aged adults (35 to 75 years old) had aneurysms detected by brain magnetic resonance angiography (MRA). In Norway, the frequency of intracranial saccular aneurysms was 1.9%, detected

* Corresponding author: *zhangningquan@shphschool.com

by MRA. The occurrence of subarachnoid haemorrhage in Norway, the same participants, was 16.4 per 100000 people per year [35].

2.1.2 Distribution in sex and age

Women are more likely to have unruptured intracranial aneurysms than men. As reported by the case study with a large number of participants, the ratio of aneurysms onset for women to men is about 3:1 [36, 37]. Furthermore, unruptured intracranial aneurysms also occur more frequently in elderly people than in young people [38], especially rare among children [39, 40]. In comparison with children patients, aneurysms in adults are likely to occur in the posterior circulation (40–45%) and in the female group (onset ratio with female patients and male patients has been estimated to be 2:1) [39, 40].

2.2 The Genetic factor of intracranial aneurysm

In most conditions, if an intracranial aneurysm occurs in people's first-degree relatives, they might have a smaller chance of suffering from intracranial aneurysms.

- There is an investigation of patients that have subarachnoid haemorrhage, only 9.4% of them have a first-degree relative that has subarachnoid haemorrhage or intracranial aneurysm, and 14% of them have a second-degree relative that suffer from those diseases.
- 193 patients' relatives underwent a screening study with subarachnoid haemorrhage aged from 20 to 70 years [41, 42]. The prevalence of first-degree relatives is only about 4% that had an unruptured intracranial aneurysm screening by MRA and intra-arterial angiography.
- When screening the first-degree relatives of patients with MRA to determine whether the occurrence of an intracranial aneurysm, if two or more members in a family once suffered from subarachnoid haemorrhage or intracranial aneurysm, the occurrence of having the diseases is the highest [43, 44]. The prevalence of intracranial aneurysm that depends on age among first-degree relatives was about 9.2% in the population that is over 30 if a family has more than two intracranial aneurysm patients.

2.3 Time of finding the intracranial aneurysm.

Half of the aneurysms are found after subarachnoid haemorrhage [45], which can occur in 6–10 per 100000 people per year.

2.4 Rupture rate of intracranial aneurysm

- There is an 8.3 years study with 130 intracranial aneurysm patients [46, 47]. If the aneurysms' diameter is less than 10mm, the aneurysmal rupture will not occur at all. However, among 51 patients with 10 mm or larger aneurysms, 15 of them suffered from a ruptured aneurysm. The frequency of rupture was 3.3% per year for aneurysms that are 10–15 mm diameter, the risk of rupture for aneurysms that are 16–25 mm diameter is about 5.6% per year, and the aneurysms that are larger than 25mm in diameter have the prevalence of rupture being 8.9% per year.
- In a cohort of 142 patients, 27 hemorrhages occurred, again with aneurysm size being a key predictor of subarachnoid haemorrhage [47]. Patients were followed up for a mean of 19.7 years [48]. The annual risk of subarachnoid haemorrhage for aneurysms less than 10 mm in diameter was 1.1% per year, and for those 10 mm in diameter or greater, the rupture risk was 2.8% per year. Cigarette smoking was an independent predictor of haemorrhage. Follow-up was subsequently extended to a median of 21 years. The mean annual incidence of rupture in this cohort was 1.1% per year. In the extended follow-up [48-50], cigarette smoking, anterior communicating artery location, and aneurysm diameter 7 mm or less were predictors of haemorrhage. On the other hand, age was inversely associated with haemorrhage. There were no ruptures after 25 years of follow-up.
- The International Study of Unruptured Intracranial Aneurysms (ISUIA) published retrospective data for patients without a history of subarachnoid haemorrhage and patients with a history of subarachnoid haemorrhage (727 to 722) [37]. There is a larger rupture rate which was 0.5% per year, for patients that has a previous experience of subarachnoid haemorrhage than those who do not have a history of subarachnoid haemorrhage, if the size of aneurysms is less than 10mm in diameter.
- During a 3-year retrospective study, there are 49 of 62 untreated patients have less than 5 mm in diameter of unruptured intracranial aneurysms [1]. The hemorrhages happened in 7 examples, and 0.9% per year was the occurrence of rupture in patients that have aneurysms less than 10 mm in diameter. If patients' aneurysms are larger than 10mm in diameter in size, 6.7% per year is the frequency of rupture.

Table 1. The summary of the different studies on intracranial aneurysm

Study of patients	Study time (years)	Rupture risk per year for <10 mm aneurysm	Rupture risk per year for >10 mm aneurysm	Rupture risk per year for 10-15 mm aneurysm	Rupture risk per year for 16-25 mm aneurysm	Rupture risk per year for >25 mm aneurysm	Affecting factors
130	8.3	0%	NA	3.3%	5.6%	8.9%	Size of aneurysm; patients' age
142	21	1.1%	2.8%	NA	NA	NA	Aneurysm's size; Cigarette smoking; anterior communicating artery location; age
1449	NA	0.5% (have the history of hemorrhage)	0.7%	NA	NA	NA	The history of haemorrhage
62	3	0.9%	6.7%	NA	NA	NA	NA

3 Diagnostic method

3.1 CT&MRI

They can identify possible aneurysms.

3.2 MRA&CTA

The occurrence and location of the aneurysm are usually found by these two devices, and they are still improving. The morphological data is offered, and they are becoming more and more sensitive. For aneurysm detection, now they can detect aneurysms that are 4mm or less in diameter.

3.3 Cerebral angiogram

The details of aneurysms are often clearly shown by the cerebral angiogram.

4 Therapies

4.1 First-generation of Pipeline Embolization Device (PED)

Parent vessel is the place where flow diverter normally implanted by covering the neck of aneurysms to change the hemodynamics, and then the inflow rate into the sac of aneurysms is reduced. As a result, thrombosis and occlusion of aneurysms can form [51, 52].

4.2 Second-generation of Derivo Embolization Device (DED)

Basic principles are similar to PED. However, the fluoroscopic visibility, flexible delivery system, and surface finishing (BlueXide) have been improved to reduce thrombogenicity [53, 54].

4.3 Super Evolve flow diverter (SE)

This is the latest method of treating the intracranial aneurysm. SE allows exclusion of the aneurysm from blood circulation without controlling intrasaccular by changing the direction of blood flow in the parent artery that is away from the aneurysm. Therefore, aneurysm thrombosis and reconstruction of the diseased artery segment can be formed [55].

5 Comparing method

The PED and DED will be compared and evaluated, respectively, and then the SE will be evaluated solely.

The PED and DED will be compared on three aspects: procedural adverse events (Hemorrhagic and thromboembolic events), rate of symptomatic complications (neurologic worsening), patients' own experience, procedure-related morbidity (neurologic worsening), and angiographic outcome (complete aneurysm occlusion and favorable occlusion) with the 6-month follow up.

The SE flow diverter will be evaluated through the aspects of samples' conditions (aneurysmal characteristics), complications, and clinical outcome.

6 PED VS DED

6.1 Samples' condition

In the reported study, there was a total number of 111 patients. PED was used in 62 of them, and the rest of them were treated by DED. For the PED group, many patients were implanted by PED many times because of different or recurrent aneurysms. The number of women was far more than the number of men in the PED group (89%) than in the DED group (84%), but the difference in age was small.

The likelihood of recurrence of aneurysms was greater in the PED group (34.2%) than that in the DED group

(14.3%). There were more fusiform aneurysms in the DED group (12.2%) than in the PED group (1.4%). Overall, the size of aneurysms was larger in the DED group (11.3mm in diameter to 14.9mm in diameter) than in the PED group (7.5mm in diameter to 5.9mm in diameter). Fortunately, the difference was not statistically significant ($P = 0.098$).

6.2 Procedural adverse events (Hemorrhagic and thromboembolic events)

The comprehensive adverse event rate was comparable between both groups (PED: 5.4%, DED: 8.2%, $P = 0.713$) according to the article [56]. Both the PED group and DED group have 3 cases that have occurred thromboembolic phenomenon, which was 4.1% risk of occurrence in the 62 patients PED group and 6.1% in the 39 patients DED group.

6.3 Rate of symptomatic complications (neurologic worsening), patients' own experience, and Procedural-related morbidity

There are a total number of 4 patients (3.2%) who developed ischemic stroke. Both the PED group and DED group have two cases, and the frequency was 2.7% in the PED group and 4.1% in the DED group. After 6 months' further research, there was no more morbidity. Consequently, the procedure-related morbidity rate was 2.7% in the PED group and 4.1% in the DED group.

6.3.1 PED group

An intradural aneurysm of the right internal carotid artery occurred in the first patient in the PED group. A serious in-stent thrombosis was exhibited by the scanning of computed tomography angiography. Then 2 overlapping PEDs were implanted in patient's vessel, but the patient's right leg suffered from minor paresis. In the center cerebral artery, there were some penetrate embolic infarctions detected by magnetic resonance imaging. After 6 months, the patient recovered.

The other patient treated by PED suffered from an intradural left-sided internal carotid artery aneurysm. Unlike the first one, the patient got minor right-sided hemiparesis after implanting the PED. The thromboembolic complications did not show initially by using the digital subtraction angiography. However, many foci of thromboembolic infarctions existed. These were detected by magnetic imaging. After 6 months' observation, the patients became almost asymptomatic.

6.3.2 DED group

The thrombus formed in the 2 patients treated by DED at the surface of the flow diverter during the process of treatment, and then it was successfully dissolved by immediate intra-arterial tirofiban administration. However, both patients exhibited postinterventional motoric aphasia, and small infarction was detected by computed tomography. Aphasia was cured fully in the first patient,

but it was resolved in the second patient after 30 days of treatment.

6.4 Angiographic outcome

After 6 months observation, complete aneurysm occlusion (OKM D) was reached in 72.6% of PED cases and 62.5% of DED cases, and favorable occlusion (OKM CpD) was 79.0% and 80.0% in each group.

7 SE flow diverter

7.1 Samples' condition

SE flow diverter was implanted in 42 patients, and the study sustained 14 months [57].

Normally the SE flow diverter was used in a wide necked aneurysm with neck ≥ 4 mm or a dome/neck ratio ≤ 2 , blister-like or fusiform aneurysms. Whether the aneurysms are ruptured or unruptured, located in the anterior or posterior circulation, pretreated, or did not pretreat, the SE flow diverter can treat all these aneurysms. However, if the patients use other types of flow diverters during the study, their data was excluded from the research.

Overall, 42 patients with 46 intracranial aneurysms were treated by SE flow diverters for 14 months. The median age of patients was 58 years, and the range of patients' age was from 28 to 84 years. The aneurysm size was 6.6mm in diameter in median (IQR 4.0–12.2 mm) with a median neck width of 4 mm (IQR 2.2–5.4 mm). About 26% of aneurysms were ≥ 10 mm (12/46), and about 85% (39/46) patients' aneurysms presented a dome/neck ratio ≤ 2 . In the overall shape, 65% (30/46) aneurysms were saccular, 22% (10/46) were fusiform, 9% (4/46) were blister, and 4% (2/46) were dissecting aneurysms. The anterior circulation was the place where about 89% aneurysms (41/46) occurred, and about 13% (6/46) aneurysms exhibited the baseline subarachnoid hemorrhage.

7.2 Complications

About 2% of (1/42) patients had a complication. During the procedure, two SE flow diverters were implanted into a large, non-ruptured fusiform paraophthalmic internal carotid aneurysm (ICA). The platelet inhibition was successful when doctors did the baseline testing, but on the final angiogram, an acute in-stent thrombosis was exhibited. Then it was resolved completely by thromboaspiration. The patient was asymptomatic after the treatment. However, the in-stent thrombosis reoccurred two weeks later. As a result, a further thrombectomy procedure is needed.

There were several moderate neurological complications that occurred in about 10% (4/42) patients: three people showed punctuate infarctions when scanning by MRI, but they did not present any neurological symptoms, and one patient had a headache for 3 weeks due to

the treatment of large aneurysm of the paraophthalmic ICA.

7.3 Clinical outcome

The mortality in the hospital was 2%, which means one patient died. The subarachnoid hemorrhage occurred in one patient on admission due to bilateral ICA. Since the initial place of bleeding could not be successful, both aneurysms were completely treated with SE in a single procedure. As a result, the bleeding was stopped. However, the patient died after 10 days because of subarachnoid hemorrhage and vasospasm. Others were cured completely and successfully by implanting the SE flow diverters, including 5 patients with ruptured aneurysms. Moreover, there were no patients who died because of the treatment of SE flow diverters.

8 Conclusion

In this review, the epidemiology, diagnostic method and effectiveness of different therapies is summarized and compared.

For the conventional treating strategies described here, the DED can be a replaced device of PED because of its dependable safety and effectiveness. Although the DED device presents comparable complication rates, morbidity, and angiographic outcome between the groups, anti-thrombogenic surface modification and improved fluoroscopic visibility of the DED did not make any improvements in regard to thromboembolic complications and fluoroscopic time, dose, and procedure time, respectively. Further research and larger observational studies are needed to find out the advantages of improved visibility and antithrombogenic surface modification.

The high technical success rate exhibits a significant improvement of SE flow diverter profile with easier navigation and deployment through a redesigned delivery system. The brand new Surpass Evolve flow diverter is likely to be an effective and efficient treating device with a favorable navigability and deployment profile. Though the short-term occlusion was successful, the efficacy of aneurysm occlusion needs to be proved in long-term follow-up studies. As a result, more research and more observation studies need to be done in the future.

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