Intracranial post-clipping residual or recurrent aneurysms: Current status and treatment options (Review)

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Abstract. Following the clipping of intracranial aneurysms, post-clipping residual or recurrent aneurysms (PCRRAs) can occur. In recent years, the incidence of PCRRAs has increased due to a prolonged follow-up period and advanced imaging techniques. However, several aspects of intracranial PCRRAs remain unclear. Therefore, the present study performed an in-depth review of the literature on PCRRAs. Herein, a summary of PCRRAs that can be divided into the following two categories is presented: i) Those occurring after the incomplete clipping of an aneurysm, where the residual aneurysm regrows into a PCRRA; and ii) those occurring after the complete clipping of an aneurysm, in which a *de novo* aneurysm occurs at the original aneurysm site. Currently, digital subtracted angiography remains the gold standard for the imaging diagnosis of PCRRAs as it can eliminate metallic clip artifacts. Intracranial symptomatic PCRRAs should be actively treated, particularly those that have ruptured. A number of methods are currently available for the treatment of intracranial PCRRAs; these mainly include re-clipping, endovascular treatment (EVT) and bypass surgery. Currently, re-clipping remains the most effective method used to treat PCRRAs; however, it is a very difficult procedure to perform. EVT can also be used to treat intracranial PCRRAs. EVT methods include coiling (stent- or balloon-assisted) and flow-diverting stents (or coiling-assisted). Bypass surgery can be selected for difficult-to-treat, complex PCRRAs. On the whole, following appropriate treatment, the majority of intracranial PCRRAs achieve a high occlusion rate and a good prognosis.

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Abbreviations: CTA, computed tomography angiography; DSA, digital subtraction angiography; PCRRA, post-clipping residual or recurrent aneurysm; EVT, endovascular treatment; ICG-VA, indocyanine green video angiography; FDSs, flow-diverting stents; STA, superficial temporal artery

Key words: post-clipping residual or recurrent aneurysms, surgical treatment, endovascular treatment

Contents

1. Introduction

Currently, treatments for intracranial aneurysms include clipping and coiling (1). Compared to coiling, the clipping of an intracranial aneurysm is associated with relatively low residual and recurrence rates (2-4). However, following the clipping of intracranial aneurysms, post-clipping residual or recurrent aneurysms (PCRRAs) can occur (5,6).

Previously, intracranial PCRRAs were considered rare; however, their incidence has increased due to prolonged follow-up periods and advanced imaging techniques (7,8). The clinical characteristics of PCRRAs are complex. For some PCRRAs, particularly for those that rupture, prompt treatment may be required, including re-clipping, endovascular treatment (EVT) and even bypass surgery (5,6,9).

Currently, little is known about PCRRAs; to date, at least to the best of our knowledge, no in-depth review has previously been published to explore intracranial PCRRAs. Therefore, in the present study, 'intracranial aneurysm', 'clipping', 'residual', 'recurrent', 'remnant', and 'recanalized' were used as search terms to retrieve related literature from the PubMed database. Subsequently, the current status and treatment options for PCRRAs were reviewed in an aim to improve the current understanding of intracranial PCRRAs.

2. Incidence

The incidence of intracranial PCRRAs varies substantially, and cases are mainly divided into recurrent cases, following complete clipping, and residual cases, following incomplete clipping (10). The incidence of PCRRAs after complete clipping

is 1.8-8.0%, and the annual incidence is 0.14-0.52% (11-14). However, not all aneurysms undergo complete clipping, even when surgeons consider that complete clipping has been achieved (Fig. 1). Of these cases, 5.2-5.9% will have residual aneurysms; the incidence of regrowth is 1.83-2.1% per year, and the total regrowth rate is 12.5-27% (14-19).

The difference in the incidence of PCRRAs is mainly related to factors, such as the length of follow-up (20). A PCRRA can occur at any point in time, and the specific timing is not clear (21). The time to occurrence may be lengthy; for instance, the average time to occurrence was 10.6 years in the study published by Kivelev *et al* (20), which is much longer than the average time to occurrence after coiling (3.3 years). Compared with intracranial post-embolization residual or recurrent aneurysms, the incidence of PCRRAs is significantly lower (22-25).

3. Pathogenesis and classification

Intracranial PCRRAs can be classified as recurrent and residual post-clipping aneurysms. The mechanisms of occurrence of these two types of intracranial PCRRAs are illustrated in Fig. 2.

Recurrent post-clipping aneurysms. There are two possible reasons that recurrent post-clipping aneurysms may occur. First, clipping may not completely correct a pre-existing weakness in the parent artery and aneurysm neck, and the aneurysm may therefore continue to grow. Second, clipping may weaken the vascular wall of the aneurysm neck and parent artery and thereby induce de novo aneurysms in these weaker regions (7,26).

Residual post-clipping aneurysms. These cases have been attributed to incomplete initial clipping or slipping of a clip after complete clipping has been achieved (20). Slipping occurs when an aneurysm neck is wide and calcified; therefore, the clip moves to the distal end of the aneurysm during clipping, causing the residual aneurysm to gradually grow under the impact of blood flow (6,27).

In addition, the risk factors for intracranial aneurysm include smoking, hypertension, dyslipidemia, diabetes, a family history of the condition, multiple aneurysms and sex (a higher incidence is observed in females), all of which are also factors that contribute to PCRRAs (21,28,29).

4. Bleeding risk

Intracranial PCRRAs are associated with a high risk of rupture of. Previous studies have reported that the incidence of bleeding is approximately 1.4-2.2% within the first decade of a PCRRA, and the incidence increases to 9-12.4% in the 20th year (5,9,30). This is far higher than the incidence of subarachnoid hemorrhage in the normal population (0.072%) (31). However, the bleeding rate of PCRRAs is lower than that in incidentally discovered unruptured aneurysms (32).

Several factors can influence whether intracranial bleeding occurs in PCRRAs, among which, the PCRRA size is the greatest risk factor. Drake and Vanderlinden (33) found that the incidence of re-bleeding was 17% in small PCRRAs, whereas it was 23% in large PCRRAs.

5. Clinical presentation

The clinical presentation of intracranial PCRRAs can be classified as ruptured or unruptured as described below:

Ruptured aneurysms. Ruptured intracranial PCRRAs are mainly characterized by headaches, nausea, vomiting, stiffness, possible limb paralysis, coma and, in severe cases, death (4). These are similar to the symptoms of the initial intracranial aneurysm rupture (34).

Unruptured aneurysms. Unruptured intracranial PCRRAs are characterized by headaches, progressive vision loss, ocular nerve paralysis, hemiplegia, dysphonia and trigeminal neuralgia (35). These symptoms are related to a variety of factors, including the size, shape and location of the PCRRA (36). However, a number of intracranial PCRRAs exhibit no symptoms or signs (37,38).

6. Imaging examination

Currently, the diagnosis of an intracranial PCRRA includes digital subtraction angiography (DSA), computed tomography angiography (CTA) and other examinations (39,40).

DSA. At present, DSA is the gold standard for the diagnosis and follow-up of PCRRAs as it can effectively exclude the influence of metallic clip artifacts (41). The diagnosis rate of three-dimensional DSA is much higher than that of two-dimensional DSA (42). Performing intraoperative DSA after aneurysm clipping, particularly in a hybrid operating room, can reduce the incidence of a PCRRA (43,44).

CTA. CTA is a novel investigation method that can be used to accurately detect intracranial aneurysms (45). Sun *et al* (46) found that CTA had a sensitivity of 71% and a specificity of 94% when detecting intracranial PCRRAs. New technology associated with CTA includes image processing with metal artifact reduction software. This process significantly reduces the metal artifacts caused by clipping in PCRRA imaging, which can improve its diagnostic rate of PCRRAs (47). In addition, detection using dual-energy CTA is less affected by clip artifacts and may thus be more effective for the diagnosis of PCRRAs with ≤2 clips (48,49).

Other inspection methods. Other than intraoperative DSA, practical indocyanine green video angiography (ICG-VA) has become one of the most widely used examination methods. ICG-VA can be used to assess blood flow through the parent artery and to determine whether residual aneurysm remains (50). Özgiray *et al* (51) treated 109 cases of intracranial aneurysms with clipping and found that ICG-VA could effectively assess the patency of the circulation. However, aneurysm remnants can occur in 6.5% cases after successful clipping (51).

7. Indications for treatment

Whether intracranial PCRRAs are treated depends mainly on certain factors, such as whether the PCRRAs are ruptured,

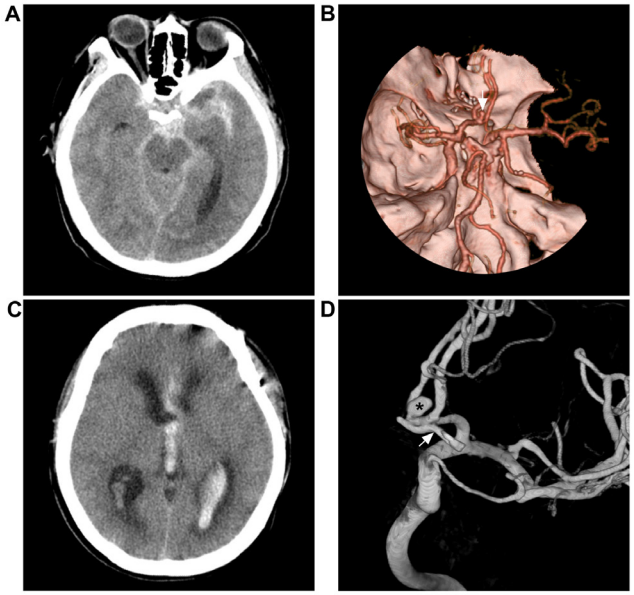

Figure 1. Repeated subarachnoid hemorrhage following incomplete clipping. (A) Head CT scan illustrating subarachnoid hemorrhage at the suprasellar cistern. (B) CTA reveals an anterior communicating aneurysm (white arrow). (C) CT scan illustrating intraventricular hemorrhage from re-rupture of the anterior communicating aneurysm recurrent two months after microsurgical clipping. (D) Angiogram illustrating the aneurysm clip (white arrow) under the remnant aneurysm (black asterisk). For the case presented, the surgeon considered that complete clipping had been achieved. CT, computed tomography; CTA, computed tomography angiography.

their necks (e.g., the width of the neck), the size and sites of the PCRRAs and the willingness of the patients and their families for treatment (35).

Bleeding. When PCRRA rupture results in bleeding, the PCRRA requires treatment (34).

Size. The size is of particular importance when selecting PCRRA treatment options. Kivelev *et al* suggested that when a PCRRA aneurysm is ≥3 mm, surgical treatment should be considered. When a PCRRA is 1-2 mm in size, it should be closely monitored (20).

Site. The treatment selected for a PCRRA is associated with its location. Jabbarli *et al* (52) examined 112 PCRRA cases and noted that the location (e.g., anterior cerebral artery > internal carotid artery > posterior circulation > middle cerebral artery) was an important risk factor for PCRRAs. Therefore, treatment should be selected when an aneurysm is in the anterior communicating artery (52).

Other factors. When PCRRAs become giant aneurysms due to thrombosis or when the rupture of the PCRRA produces an intracranial hematoma resulting in space occupying effect, craniotomy should be seriously considered (53).

8. Treatment options

A number of treatment options are available for PCRRAs, mainly including re-clipping of the aneurysm, EVT and bypass surgery (53).

Clipping. Re-clipping remains the main method used for the treatment of PCRRAs. This procedure is much more difficult to perform than the initial clipping, mainly as the scarred and adhered brain tissue renders the exposure of the operative field and the parent artery difficult, and the previously placed clip interferes with the ability to expose the aneurysm neck. Additionally, intraoperative rebleeding can occur while the existing clip is being moved (7,20,54). The re-clipping of an intracranial PCRRA should proceed according to the following sequence: Dissection toward the aneurysm, bypass assistance if necessary, mobilization of the existing clip and placement of the new clip(s) (7,20).

Among the events mentioned above, whether to move the existing clip during re-clipping is a key decision that must be made; in addition, previous studies have proposed that it is beneficial to move an existing aneurysm clip in order to allow sufficient space in which to operate (55,56). However, another study did not suggest the intraoperative removal of an existing aneurysm clip as this may cause a tear in the aneurysm (57). Therefore, whether an existing clip is moved should be determined based on the needs of the procedure.

In addition, if the PCRRA is large in size or contains a thrombosis, it can be cut after the PCRRA is trapped. The presence of a thick and atherosclerotic aneurysm wall may necessitate the suturing of the edges of the incised sac to facilitate clip placement at the neck (20).

EVT. Currently, EVT is the main effective treatment method for PCRRAs (58). It also has a higher success rate for blocking PCRRAs. Gross *et al* (59) described 43 cases of intracranial PCRRAs in which EVT was used, and they found that 79% of the PCRRAs were completely occluded, 14% had residual neck tissue and 7% had stable small dome residues. A number of EVT methods are available for the treatment of intracranial PCRRAs, including coiling (or stent- or balloon-assisted methods) and flow-diverting stents (FDSs) (or coil embolism-assisted) (60-63).

Single coiling is the most practical method to treat an intracranial PCRRA, particularly for PCRRAs with a narrow neck (Fig. 3). Gross *et al* (59) used single coiling in 18 cases of narrow-neck PCRRAs and observed no recurrence during an average follow-up period of 3.9 years. However, in wide-necked, large, complex PCRRAs, stent- or balloon-assisted EVT is required (61,64,65). The recanalization rate is high in complex PCRRAs (66).

FDSs are a new type of stent that has emerged in recent years that can effectively treat intracranial PCRRAs. An FDS is a flexible, low-porosity, endoluminal stent that is capable of altering the hemodynamics of the parent artery and aneurysm, resulting in the formation of a thrombosis in the aneurysm. FDSs can also guarantee blood flow through the normal para-aneurysm branch and are therefore especially suitable for large, wide-neck PCRRAs (67,68). For instance, in a previous study, seven cases of PCRRA were treated by Adeeb *et al* (8), and all were completely embolized without sequelae following the implantation of FDSs.

However, the treatment of a PCRRA using FDSs often requires a longer time to achieve complete occlusion. For example, Dornbos *et al* (69) performed FDS implantation in

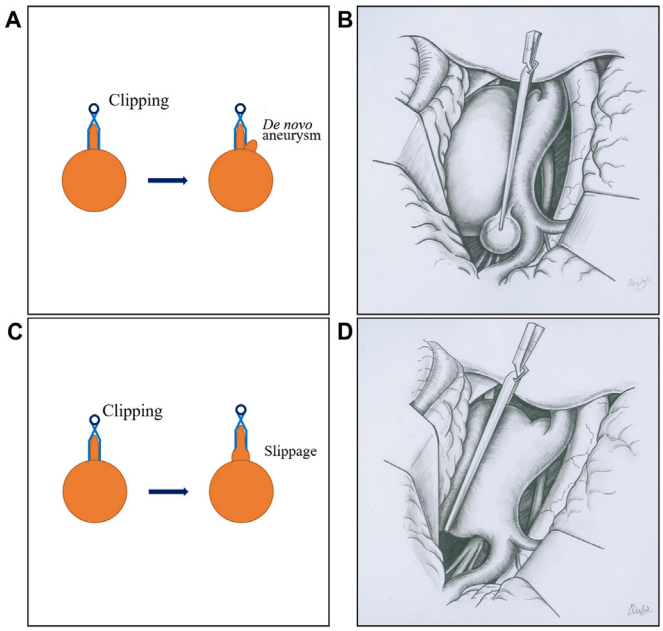

Figure 2. Classification of intracranial PCRRAs. (A and B) Images show the development of a *de novo* aneurysm after clipping. (C and D) Images show a post-clipping residual aneurysm due to clip slippage. PCRRAs, post-clipping residual or recurrent aneurysms.

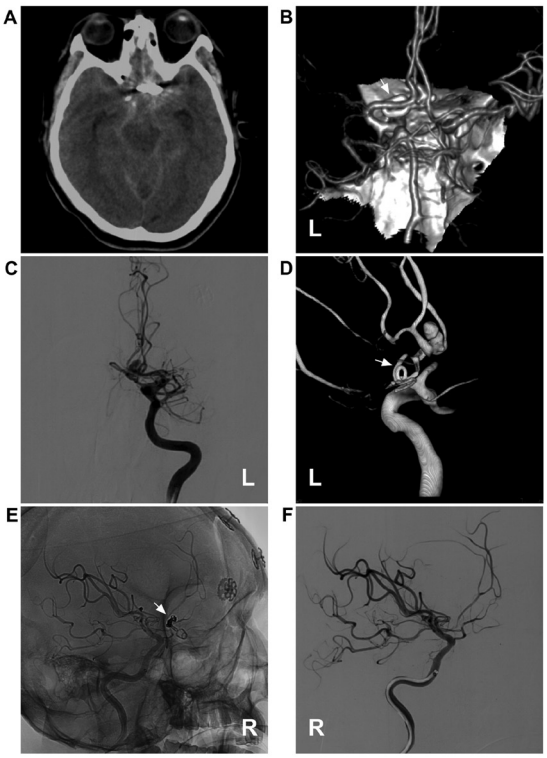

Figure 3. Coiling of the post-clipping recurrent aneurysm. (A) Brain CT scan illustrating subarachnoid hemorrhage at the suprasellar cistern; a metallic artefact can be seen. (B) Brain CTA illustrating the recurrent anterior communicating aneurysm; the clip can be seen (white arrow). (C) DSA of the left internal carotid artery illustrating the moyamoya-like vessels in the region of middle cerebral artery. (D) Three-dimensional DSA illustrating the recurrent anterior communicating aneurysm and the clip (white arrow). (E) Unsubtracted and (F) subtracted angiogram illustrating that the aneurysm is coiled completely. For the case presented in the image, the first clipping was performed five years ago. CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; L, left; R, right.

four cases of intracranial PCRRAs, and post-operative DSA revealed that 80% of the PCRRAs had embolized at six months post-operatively, while 100% had embolized at 12 months post-operatively.

Bypass surgery. Bypass surgery is considered as a 'last resort' for the treatment of complex PCRRAs that are difficult to treat (20). Bypass surgery can be divided into three categories according to its purpose, as follows: i) To provide permanent and adequate blood flow for the distal parent artery of the PCRRA; ii) to prevent cerebral ischemia caused by the temporary occlusion of the parent artery; and iii) to isolate the PCRRA and reconstruct the parent artery (53).

The selection of bypass surgery that is most appropriate depends on the individual case. Kivelev *et al* (20) described 25 cases of intracranial PCRRA in which bypass treatment was applied, including clipping of PCRRAs with bypass treatment, PCRRA trapping with bypass treatment and proximal occlusion of PCRRAs with bypass treatment. Over an average post-operative follow-up period of 3.5 years, 23 patients exhibited a good prognosis, and their modified Rankin scale score was <2 points (20).

During bypass surgery for intracranial PCRRAs, the most commonly used supply arteries include the following: i) The superficial temporal artery (STA) and the occipital artery, both of which are suitable for middle- and low-flow bypass surgery; and ii) the radial artery and the great saphenous vein (required to connect the external carotid system), which are ideal interposition grafts for high-flow bypass surgery (20,70-72).

9. Treatment outcomes

The treatment of PCRRAs can achieve satisfactory outcomes (55,73,74). As regards the occlusion rate in the treatment of PCRRAs, the rate of complete obliteration has been shown to be 72-89, and 84% of the patients have been shown to have a good functional outcome (55,61,73,74). Moreover, no evidence is currently available to confirm that treatment results are related to the size and sites of PCRRAs or to whether surgical clipping and EVT are used (61).

The surgical clipping of PCRRAs requires the adhered tissues to be stripped, resulting in repeated brain injury. Therefore, these procedures are much more difficult to perform and involve several complications, including cerebral infarction, meningitis and epilepsy (53). Drake *et al* (74) reported that the disability rate was 7% and the mortality rate was 5.2%. Giannotta and Litofsky (55) reported a mortality rate of 15.8%, which was higher than that reported in the study by Drake *et al* (74).

EVT produces less damage to the brain and has a significantly lower risk of post-operative complications than clipping (20,21). Gross *et al* (59) described 60 PCRRA patients who were treated with EVT, and the post-operative procedural permanent morbidity and mortality rates were only 3 and 2%, respectively. Li *et al* (75) performed EVT in 43 cases of intracranial PCRRA, 36 (84%) of which had complete occlusion, and no re-bleeding occurred during the follow-up period (average, 34.5 months).

In conclusion, in the majority of intracranial PCRRAs, active treatment results in a high occlusion rate and an improved clinical prognosis.

10. Conclusions

After an intracranial aneurysm is clipped, in some cases, PCRRAs can occur. Symptomatic PCRRAs require prompt treatment, particularly those that have ruptured. A number of treatment methods are available for intracranial PCRRAs, mainly including re-clipping and EVT. Bypass surgery can be selected for difficult-to-treat, complex PCRRAs. Following appropriate treatment, the majority of intracranial PCRRAs can achieve a high occlusion rate and an improved prognosis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JY and JP designed the study and drafted the manuscript. TL and LQ collected and analyzed the clinical data. JY and JP confirm the authenticity of all the raw data. JY critically revised the manuscript. LQ constructed and prepared the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was not required for the present review article from our institution. Written informed consent was obtained from the patients whose data are depicted in the figures.

Patient consent for publication

Written informed consent was obtained from the patients for publication of the relevant information.

Competing interests

The authors declare that they have no competing interests.

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