CLIP ligation of an aneurysm neck is believed to be the most durable treatment modality for aneurysm exclusion from circulation. The evolution of potentially safer and less invasive endovascular therapies has encouraged more objective assessments of microsurgical clip ligation and its benefits. Even with postoperative confirmation of complete obliteration, patients may be at a continued risk for recurrent aneurysms and the development of de novo aneurysms. Aneurysm recurrence may be due to radiographically unapparent or incomplete initial obliteration, clip slippage/breakage, or regrowth. The efficacy of clip ligation is high, and annual recurrence rates of 0.26% to 0.53% have been reported. In addition, de novo aneurysms have been reported to occur at a rate of 0.84% to 1.8% per year.

Long-term angiographic study of surgically treated aneurysms and the development of de novo aneurysms. Aneurysm recurrence may be due to radiographically unapparent or incomplete initial obliteration, clip slippage/breakage, or regrowth. The efficacy of clip ligation is high, and annual recurrence rates of 0.26% to 0.53% have been reported. In addition, de novo aneurysms have been reported to occur at a rate of 0.84% to 1.8% per year.

- **KEY WORDS**  
  aneurysm; clip ligation; recurrence; follow-up; angiography; subarachnoid hemorrhage; vascular disorders

**OBJECTIVE**  
With the recent evolution of endovascular therapies, objective evaluation of the efficacy of clip ligation for cerebral aneurysms should be performed. This study was undertaken to evaluate the durability of microsurgical clip ligation, identify risk factors for recurrence, and assess the need for long-term follow-up imaging.

**METHODS**  
A retrospective review of medical records identified 616 consecutive patients (156 male and 460 female patients; mean age 48.4 ± 12.4 years; range 6–90 years) who underwent microsurgical clip ligation and follow-up imaging at least 1 year after discharge between 1990 and 2010 at our institution. Of a total of 926 aneurysms in 616 patients, 758 aneurysms were microsurgically clip-ligated. At presentation, 431 of these aneurysms were ruptured and 327 aneurysms were unruptured. All patients underwent postoperative baseline imaging within the 1st month of their operation. A logistic regression analysis was performed to identify which variables are more likely to predict recurrence.

**RESULTS**  
Late follow-up angiographic imaging was obtained at a mean of 7.2 ± 4.7 years postdischarge (median 5.7 years; range 1–23 years). Of the 699 clipped aneurysms without residua, late follow-up angiography revealed only 1 (0.14%) recurrent aneurysm. Of the 59 residual aneurysms that remained after initial clip ligation on early postoperative imaging, 8 (13.6%) demonstrated growth. All of these aneurysms required treatment. None of the recurrences were due to broken or delayed displacement of clips. A total of 111 patients presented with multiple aneurysms. De novo aneurysm formation occurred in 8 (0.97%) patients, all of whom initially presented with multiple aneurysms.

**CONCLUSIONS**  
This study provides additional evidence to support the long-term efficacy of aneurysm clip ligation. The chance of aneurysm recurrence after complete clip ligation is very small. However, there is a regrowth risk of 1.83% per year for aneurysm remnants after incomplete clip ligation. These findings support the necessity for continued follow-up, late angiographic imaging, and the potential need for further intervention of incompletely ligated aneurysms. Furthermore, completely clip-ligated aneurysms may not require additional surveillance imaging unless multiple aneurysms were evident at presentation.

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eurysms has been used to monitor recurrence.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\) Currently, there is no established standard protocol for the timing or length of follow-up after microsurgical treatment. The known risk factors associated with aneurysm formation include hypertension, smoking, middle age, and female sex.\(^7\)\(^,\)\(^8\) Tsutsumi et al. identified the presence of multiple aneurysms at initial presentation and residual aneurysm after clip ligation as important risk factors for recurrence.\(^19\)

An objective evaluation of the long-term durability of clip ligation is one of the factors that is pertinent for justifying the use of microsurgery. With improvement in the long-term efficacy of embolization, more knowledge is needed regarding the true recurrence rates after clip ligation and the risk factors for aneurysm recurrence. These data are vital to providing the patient with reliable information so the most appropriate decisions regarding aneurysm management can be made. We have made a special effort to carefully monitor our patients during the past 3 decades, and this study was undertaken to assess the risk of aneurysm recurrence following microsurgery.

**Methods**

**Patient Population**

The institutional review board of Indiana University approved this study. We have prospectively maintained a neurovascular database of all our patients suffering from cerebral aneurysms since 1976. We performed a retrospective single-institution study of all patients who harbored a cerebral aneurysm and underwent microsurgical clipping. To effectively analyze the long-term viability of clip ligation, we focused our search on 1990 to 2010 and identified 1785 patients who underwent microsurgery. During this time period, we employed relatively uniform and modern microsurgical techniques. Of the 1785 patients, 616 had returned at least for their 1-year follow-up (mean age 48.4 ± 12.4 years; age range 6–90 years). We defined “long-term follow-up” as ≥1 year after the initial surgical treatment. Patients with an associated arteriovenous malformation or those who underwent primary parent vessel occlusion were excluded.

Within the cohort of 616 patients who underwent long-term follow-up imaging, 926 aneurysms received treatment, of which 758 were clip-ligated. We collected demographic, perioperative complication, and outcome data to assess the durability of microsurgery. We used intraoperative angiography frequently during the study period. The majority of residual aneurysms were known on intraoperative angiography; however, further clip repositioning was deemed unsafe due to the vascular anatomy and location of the branching and perforating vessels.

We reviewed all the available digital subtraction angiography (DSA) or CT angiography (CTA) reports to confirm the presence of an aneurysm preoperatively and the status of the aneurysm postoperatively and during the follow-up visits. During the study period, all patients underwent postoperative baseline DSA (or CTA in rare cases) within the 1st month of their surgery. CTA, and rarely DSA, was used to assess aneurysm recurrence or the development of de novo aneurysms during the follow-up period.

Surgical outcomes were stratified based on the presence of residual aneurysm after surgical treatment. We defined a recurrent aneurysm as an aneurysm that was completely clip-ligated but displayed regrowth on follow-up imaging. Residual aneurysm is defined as an aneurysm that was incompletely clip-ligated with a small remnant remaining between the parent vessel and the base of the clip. We defined regrowth as an increase in the size of the aneurysm remnant on follow-up imaging compared with the immediate postoperative imaging. Aside from regrowth and the residuum of the aneurysm, we also studied the development of a new aneurysm at a location other than the original site of the presenting aneurysm, which was referred to as a de novo aneurysm.

**Statistical Analysis**

Data analysis was performed using the Statistical Package for Social Sciences (version 19) and Microsoft Excel (2010). Data are presented as the means ± standard deviations. Statistical significance was defined as a p value < 0.05. Annual rates of aneurysm regrowth were calculated by dividing the number of enlarged aneurysms after incomplete obliteration by the average number of years until the last angiographic imaging follow-up.

We performed logistic regression analysis to predict which variables were more likely to predict recurrence or regrowth. Sex, age, aneurysm location, multiplicity, and presence of aneurysmal subarachnoid hemorrhage (SAH), hydrocephalus, postoperative neurological deficits, and smoking status at the time of initial admission were taken as predictor variables. We also performed a chi-square analysis to identify any relationship between a predictor variable and the probability of regrowth.

In this study, participating surgeons could have unknowingly selected the patients with no residuals to be monitored less frequently compared with the patients with remnants. To identify if this physician bias could have influenced our results, we performed a 1-way ANOVA with imaging years as the independent variable against the development of recurrence or regrowth.

**Results**

Of the 616 patients who underwent microsurgical clip ligation, there were 59 (7.8%) aneurysms with a residual neck and 699 (92.2%) aneurysms without a residual neck on postoperative imaging. The patient demographics at the time of initial admission are summarized in Table 1. Relevant clinical data are presented in Table 2. Of the 699 clipped aneurysms without residua, late follow-up angiography revealed only 1 (0.14%) recurrent aneurysm. Of the 59 residual aneurysms after initial clip ligation identified on early postoperative imaging, 8 (13.6%) demonstrated regrowth; all of these aneurysms required treatment. None of the recurrences or regrowths were due to the broken clips or delayed displacement. A total of 111 patients presented with multiple aneurysms.

Our analysis revealed nonsignificant associations between being a smoker at initial admission (p = 0.401), sex (p = 0.555), presence of aneurysmal SAH (p = 0.136), multiplicity of aneurysms (p = 0.560), hypertension (p = 0.705), and aneurysm recurrence or regrowth. Late follow-
up angiographic imaging was obtained at a mean of 7.2 ± 4.7 years postdischarge (median 5.7 years; range 1–23 years). The duration of follow-up for individual groups are summarized in Table 3. Treatment specifics are mentioned in Table 4.

Patients With Residual Aneurysm on Early Postoperative Imaging

Of the 59 patients with residual aneurysm, 8 (13.6%) aneurysms enlarged and 51 (87.3%) remained stable on long-term follow-up imaging. Among the 51 stable aneurysms, 29 (56.9%) presented with SAH, while 22 (43.1%) were unruptured. Of these, 44 (86.3%) aneurysms were located on the anterior circulation and 7 (13.7%) on the posterior circulation. None of the patients with stable residual aneurysms presented at follow-up with neurological symptoms or rehemorrhage.

In the 8 aneurysms that progressed, 4 (50%) initially presented with SAH, and 4 (50%) were unruptured. Three patients presented with neurological symptoms, including headaches, on follow-up imaging that revealed the growth of a partially clipped aneurysm, and 5 were found on surveillance imaging. None of the residual aneurysms that grew rehemorrhaged. The specific locations for these aneurysms were as follows: 2 aneurysms on the middle cerebral artery, 1 aneurysm on the anterior communicating artery complex, 2 aneurysms on the posterior communicating artery, 2 aneurysms on the ophthalmic artery, and 1 aneurysm on the internal carotid artery. Of the 8 aneurysms that progressed, 2 (25%) were in patients who initially presented with multiple aneurysms. There was a regrowth risk of 1.83% per year for aneurysm remnants after incomplete clip ligation.

Patients Without Residual Aneurysm on Early Postoperative Imaging

Only 1 (0.14%) patient suffered from a recurrence. This 34-year-old male patient initially presented with a right proximal A1 segment aneurysm that was clip-ligated. Follow-up imaging revealed de novo aneurysm formation on the dysplastic left proximal A1 segment that was subsequently also clipped. An immediate postoperative DSA did not reveal any residual aneurysm. This de novo aneurysm exhibited recurrence on follow-up angiography 5 years later.
De Novo Aneurysm Formation

A total of 111 (18.0%) patients presented with multiple aneurysms on admission, and 8 patients demonstrated de novo aneurysm formation during the follow-up period. There was no de novo aneurysm identified in any patient who presented with a single aneurysm on the initial admission.

Discussion

We analyzed cerebral aneurysm clip durability and “long-term” (> 1-year postdischarge) outcomes. Few studies exist that address the necessity of follow-up angiography and the efficacy of clip ligation. Although postoperative angiography can confirm initial aneurysm obliteration, the potential for clip failure and aneurysm recurrence or regrowth still remains. Recent data suggest that neither endovascular nor surgical treatments can fully eliminate the risk of aneurysm recurrence, residua growth, or SAH. In addition, some aneurysms cannot safely undergo complete exclusion because of the surrounding vascular anatomy/dysplasia and the presence of branching and perforating arteries.

A similar study from a statewide California database featured a long-term follow-up study of unruptured intracranial aneurysms that underwent endovascular coiling (n = 944) and clip ligation (n = 1565); 76 aneurysms received combination treatment. In this study, the follow-up period included a median of 7 years (range 4–12 years). Intracranial hemorrhage occurred in 5.9% of clipped and 4.8% of coiled aneurysms, and 193 (20.4%) patients with coiled aneurysms underwent additional aneurysm repair compared with 136 (8.7%) of patients with clipped aneurysms. The study observed no perioperative survival advantage for coiling on long-term follow-up, while the postoperative aneurysm rupture rates were similar for both clipping and coiling procedures.

The recurrence rates after coil embolization may be as high as 30% to 40% with long-term (> 1 year) follow-up, even after near-complete, initial aneurysm occlusion. Most recently, Chalouhi et al. assessed long-term angiographic results after coil embolization in 209 patients who initially harbored adequately occluded aneurysms. In their 209 patients, there was a 41% recurrence rate with long-term angiographic follow-up (defined as > 36 months). Specifically, 32% of patients who originally demonstrated no residuum on short-term angiography developed aneurysm recurrence after 36 months, and 67% of those with minimal recurrence showed significant regrowth on long-term follow-up assessment. Furthermore, 26% of the 209 patients required repeated interventions due to recurrence. These data suggest that long-term imaging is needed after endovascular coil treatment and that a substantial percentage of patients will require repeat treatment. However, the risk of hemorrhage from aneurysm regrowth after coil embolization is small.

Obliteration efficacy has become a crucial factor for evaluating the improvement of endovascular techniques in treating ruptured and unruptured cerebral aneurysms. Ogilvy et al. recently developed and validated the first comprehensive model that quantitatively predicts retreatment risk following endovascular therapy. This aneurysm

<table>
<thead>
<tr>
<th>TABLE 3. Postoperative outcomes*</th>
<th>Residual Aneurysm (n = 59)</th>
<th>No Residual Aneurysm (n = 699)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Progressive (n = 8)</td>
<td>Stable (n = 51)</td>
</tr>
<tr>
<td>GOS score at last follow-up</td>
<td>1</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (25)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Mean ± SD follow-up period</td>
<td>7.4 ± 4.6</td>
<td>7.3 ± 4.5</td>
</tr>
<tr>
<td>Median</td>
<td>8.1</td>
<td>6.8</td>
</tr>
<tr>
<td>Range</td>
<td>1–15</td>
<td>1–20</td>
</tr>
<tr>
<td>Radiography</td>
<td>Angiography</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>CTA</td>
<td>3 (37.5)</td>
<td>33 (67.7)</td>
</tr>
</tbody>
</table>

GOS = Glasgow Outcome Scale.
* Values are presented as number of aneurysms (%) unless otherwise indicated.

<table>
<thead>
<tr>
<th>TABLE 4. Clip treatment*</th>
<th>Residual Aneurysm (n = 59)</th>
<th>No Residual Aneurysm (n = 699)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Progressive (n = 8)</td>
<td>Stable (n = 51)</td>
</tr>
<tr>
<td>Single clip</td>
<td>8 (100)</td>
<td>28 (54.9)</td>
</tr>
<tr>
<td>Multiple clip</td>
<td>0</td>
<td>23 (45.1)</td>
</tr>
<tr>
<td>Trap bypass</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clip, immediate coil</td>
<td>1 (12.5)</td>
<td>5 (9.8)</td>
</tr>
</tbody>
</table>

* Some aneurysms may have undergone multiple treatment modalities. Values are shown as number of aneurysms (%) unless otherwise indicated.
recanalization stratification scale takes into account the initial treatment results and the aneurysm- and treatment-related factors from a multicenter cohort of 1543 patients. Points are assigned to each factor, and the scale serves as a valid prognostic index.14

Although small, there exists a risk of aneurysm rehemorrhage after coil embolization when compared with clip ligation. The International Subarachnoid Aneurysm Trial (ISAT) randomly assigned 2143 patients with ruptured intracranial aneurysms to either clip ligation or coil embolization treatment groups. Twenty-four rebleeds occurred during the long-term follow-up period (mean 9 years; range 6–14 years). For the rebleeds that occurred in the endovascular and clip-ligated groups, 10 (0.93%) and 3 (0.28%) occurred at the target aneurysm, respectively. Other causes of recurrent SAH were due to additional untreated aneurysms, de novo aneurysms, or undetermined etiology.12

Complementing the ISAT study is the Barrow Ruptured Aneurysm Trial (BRAT): the 6-year results analyzed the safety and efficacy of clip ligation and coil embolization in patients who presented with an aneurysmal SAH. Spetzler et al. randomly assigned a total of 408 patients to receive either clipping (n = 209) or coiling (n = 199). Those who were treated with clip ligation achieved a complete aneurysm obliteration rate of 96% (111 of 116 patients), whereas those treated with coiling achieved an obliteration rate of 48% (23 of 48 patients). The overall results after 6 years thus far demonstrate no major difference in outcomes between clip ligation and coil embolization for the treatment of anterior circulation aneurysms. For posterior circulation aneurysms, however, coil embolization led to superior outcomes compared with clipping. Patients who underwent coiling had significantly lower obliteration rates and significantly higher retreatment rates than those who received clip ligation.17

Data regarding long-term angiography after clip ligation in order to monitor recurrence have been limited to date. To evaluate recurrence, de novo formation, and patient outcome, David et al. conducted a late angiographic follow-up review of 102 patients who had undergone clip ligation for their 147 aneurysms.3 Follow-up evaluations were obtained at a mean of 4.4 ± 1.6 years postsurgery (range 2.6–9.7 years). Of the 135 (91.8%) clipped aneurysms without initial residua, 2 (1.5%) recurred on late follow-up angiographic imaging. On immediate postoperative angiography, 12 (8.2%) clipped aneurysms had residua, and 2 (16.7%) of these demonstrated progression on later follow-up visits. Six patients developed 8 de novo aneurysms, yielding an annual rate of 1.8% per year.3 This late angiographic follow-up review was the first study to analyze patient outcomes and confirm the long-term efficacy of aneurysm clip ligation. Similar to our findings, the authors of this study also concluded that, because of the low incidence of recurrence for completely obliterated aneurysms, late follow-up imaging for these patients might not be warranted. Our study features the largest cohort and longest follow-up data to date and supports this recommendation.

The accurate detection of aneurysm recurrence cannot be performed without high-resolution angiographic imaging. Our follow-up imaging protocol depended on the sensitivity and specificity of CT angiography for identifying a residual aneurysm neck, small changes in aneurysm size, and new aneurysm formation. A recent meta-analysis study by Sun et al. evaluated the diagnostic accuracy of CTA in comparison with catheter angiography for identifying residual or recurrent cerebral aneurysms after clip ligation. This report included 10 studies with a total of 487 aneurysms. The pooled results confirmed CTA to have 71% sensitivity and 94% specificity for identifying residual or recurrent aneurysms.18

Overall, our study suggests that patients who undergo complete clip ligation of their aneurysm and harbor only a single aneurysm at the time of initial admission may not need to undergo follow-up imaging. However, patients with residual aneurysms or multiple aneurysms, regardless of the status of their clipped aneurysms, deserve long-term follow-up surveillance.

New or de novo aneurysms are occasionally discovered in patients suffering from another aneurysm in a different location. This type of aneurysm may have an increased risk of SAH. Moreover, women, current smokers, and patients with a history of multiple aneurysms have a significantly increased likelihood of de novo aneurysm formation.3,8,12 This information indicates that patients with multiple aneurysms would require closer long-term follow-up surveillance imaging and potentially more aggressive therapy. Our previous study quantified the risk of hemorrhage among patients with de novo cerebral aneurysms. We estimated the 5-year risk of SAH in these patients with de novo aneurysms to be 2.9% per year.9

Study Biases and Limitations

Similar to other retrospective studies, our study is subject to weaknesses and biases. Incompletely clipped aneurysms may have undergone more careful surveillance imaging, leading to a higher risk of regrowth detection among these patients. However, our analysis revealed no significant difference in the number of postoperative imaging years and the development of aneurysm regrowth among the patients who had completely or partially clipped aneurysms (p = 0.795). This finding suggests that physician bias most likely had no significant influence on the results in our study.

There is also a follow-up bias, as not all patients were evaluated at or for the same time intervals, although we attempted to perform DSA within the first month of surgery and complete CTA imaging at 1 year and every 5 years after clip ligation. A reasonable number of our patients were also lost to follow-up.

Aneurysm recurrences and regrowth could potentially be due to the delayed displacement of their associated clips. Although our review did not seem to indicate the occurrence of clip slippage, this phenomenon cannot be reliably ruled out.

The makeup of this group may not be representative of our entire population and confounds our final results. A prospective study could eliminate the aforementioned biases. It is also unlikely that the logistic regression analysis would have retrieved significant p values given the lack of variability within the data among the groups with or with-
out recurrence. In our present study, there were 9 patients with recurrence or regrowth and 607 patients without recurrence. This lack of equal sample sizes could have reduced the probability of retrieving a significant p value in logistic regression. Nemes et al. reports that small sample sizes can overestimate the odds ratios and may lead to unreasonable conclusions. This lack of equal sample sizes could have led to overestimated odd ratios and resulted in nonsignificant p values, even though there is evidence of an association between the predictor variables in an actual clinical setting and the probability of aneurysm regrowth.

Conclusions

This retrospective study provides additional evidence to support clip ligation as a durable treatment modality for aneurysm management. Our results demonstrated a low recurrence rate of 0.14% among completely clip-ligated aneurysms and a 13.6% rate of regrowth in aneurysms with remnants on early postoperative imaging. Incompletely clip-ligated aneurysms that displayed residuum on postoperative imaging have a risk of regrowth of 1.83% per year. Patients suffering from multiple aneurysms are at increased risk of de novo aneurysm formation.

Based on our findings, we recommend late angiographic follow-up for 2 groups of patients: those who have residual aneurysms on postoperative imaging, and those who present with multiple aneurysms on admission regardless of the status of their clipped aneurysms. Late angiographic follow-up is most likely unnecessary for patients whose single aneurysm was completely clip-ligated, as confirmed on postoperative catheter angiography.

References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: M. Cohen-Gadol. Statistical analysis: Cohen-Gadol, Guandique, Horner, Kim.

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