Effect of Age on Outcomes of Treatment of Unruptured Cerebral Aneurysms
A Study of the National Inpatient Sample 2001–2008

Waleed Brinjikji, BS; Alejandro A. Rabinstein, MD; Giuseppe Lanzino, MD; David F. Kallmes, MD; Harry J. Cloft, MD, PhD

Background and Purpose—Age might differentially affect outcomes in patients treated for unruptured cerebral aneurysms with surgical clipping versus endovascular coil therapy. We evaluated a large administrative database to determine the effect of age on outcomes in patients treated for unruptured cerebral aneurysm.

Methods—Using the National Inpatient Sample, we evaluated morbidity (discharge to long-term facility) and mortality of patients undergoing clipping or coiling of unruptured cerebral aneurysms in the United States between 2001 and 2008. Outcomes were evaluated in relation to four age strata: younger than 50 years; 50 to 64 years; 65 to 79 years; and patients 80 years or older.

Results—Patients younger than 50 years old undergoing coiling had significantly lower morbidity rates when compared to patients who underwent clipping (3.5% versus 8.1%; P<0.0001), but no difference in mortality (0.6% versus 0.6%; P=0.72). Patients between 50 and 64 years old undergoing coiling had significantly decreased morbidity (4.0% versus 13.7%; P<0.0001) and mortality (0.5% versus 1.1%; P<0.0001) when compared to patients who underwent clipping. Coiled patients 65 to 79 years old had lower morbidity (6.9% versus 26.8%; P<0.0001) and mortality (0.8% versus 2.0%; P<0.0001) compared to patients who underwent clipping. Patients aged 80 years or older undergoing coiling also had lower morbidity (9.8% versus 33.5%; P<0.0001) and mortality (2.4% versus 21.4%; P<0.0001) when compared to patients who have undergone clipping.

Conclusions—Patients treated with endovascular coil have significantly less morbidity and mortality than those treated with surgical clipping, and these differences become more pronounced with age. (Stroke. 2011;42:1320-1324.)

Key Words: endovascular treatment ■ interventional neuroradiology ■ intracranial aneurysm ■ outcomes

Physicians choose between surgery, endovascular treatment, and observation for patients presenting with unruptured intracranial aneurysms. Because the risk of subarachnoid hemorrhage resulting from an unruptured aneurysm is relatively low, the risks associated with surgical or endovascular treatment must be quite low for treatment to be justified. Previous studies have demonstrated that increasing age has a negative effect on outcomes of both surgical and endovascular treatment of cerebral aneurysms.1,2 Because surgical treatment of unruptured intracranial aneurysms is more invasive, it might be expected to result in worse outcomes than endovascular treatment in elderly patients. The United States National Inpatient Sample (NIS) has been used previously to study outcomes of patients treated for unruptured cerebral aneurysms3–7 and provides data that can be used to evaluate the effect of age on outcome. In this study, we applied the NIS data from 2001 to 2008 to determine and compare outcomes of clipping and coiling of intracranial aneurysms in the elderly.

Patients and Methods

Patient Population
We purchased the NIS hospital discharge database for the period 2001 to 2008 from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, Rockville, Maryland. The NIS is a hospital discharge database that represents 20% of all inpatient admissions to nonfederal hospitals in the United States.

All patients had a diagnosis of unruptured aneurysm (code 437.3 in the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]) and an ICD-9-CM procedure code of “clipping of aneurysm” (ICD-9-CM code 39.51) or of coiling of aneurysm, which included “other repair of aneurysm” (ICD-9-CM code 39.52), “endovascular repair or occlusion of head and neck vessels” (ICD-9-CM code 39.72) and “other endovascular repair (of aneurysm) of other vessels” (ICD-9-CM code 39.79). We excluded patients with “subarachnoid hemorrhage” (ICD-9-CM code 430) and “intracerebral hemorrhage” (ICD-9-CM code 431). We stratified patients into 4 age groups: patients younger than 50 years; patients 50 to 64 years; patients 65 to 79 years; and patients 80 years or older.

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Comorbidities
We collected data on the following comorbidities: obesity (ICD-9-CM code 278.00 to 278.01), alcohol abuse (ICD-9-CM code 305.00 to 305.02), anemia (ICD-9-CM code 280.0 to 283.0), congestive heart failure (ICD-9-CM code 428.0 to 428.9), valvular disease (ICD-9-CM code 394.0 to 397.9), hypertension (ICD-9-CM code 401.0 to 405.99), drug abuse (ICD-9-CM code 304.00 to 304.9), diabetes mellitus (ICD-9-CM code 250.0 to 250.9), cancer (ICD-9-CM code 140.0 to 2089.1), anemia (ICD-9-CM code 280.0 to 283.0), chronic liver disease (ICD-9-CM code 286.0 to 287.9), psychiatric disorder (ICD-9-CM code 293.81 to 3029), chronic renal disease (ICD-9-CM code 584.6 to 586), coagulopathy (ICD-9-CM code 986.9), peptic ulcer disease (ICD-9-CM code 533.00 to 533.9), and malignancy (ICD-9-CM code 1400 to 2089.1). Mean number of comorbidities for each group was calculated.

End Points
The two primary end points of this study were discharge to long-term facility and in-hospital mortality. Discharge status and mortality were studied by using the Healthcare Cost and Utilization Project-NIS Discharge Status and Mortality Module. Variables analyzed included age group, gender, race (white versus non-white), treatment modality (clipping versus coiling), and the comorbidities listed. To obtain national estimates, proper weights were applied as indicated in the Healthcare Cost and Utilization Project-NIS Calculating NIS Variances Guide. All statistical analysis was performed using the SAS-based statistical package JMP (www.jmp.com).

Results
Patient Demographics
Between 2001 and 2008, a total of 34054 patients underwent clipping of unruptured intracranial aneurysms and 29886 patients underwent clipping of unruptured intracranial aneurysms. For clipped patients, 77.3% (26303/29886) were white versus 76.5% (22858/34049) coiled patients. For clipped patients, 74.7% (22315/29886) were female versus 75.2% (25600/34049) for coiled patients. Of patients undergoing clipping of unruptured intracranial aneurysms, 10195 patients (29.9%) were younger than 50 years old, 13862 patients (40.7%) were between 50 and 64 years old, 9178 (26.9%) were between 65 and 79 years old, and 809 (2.4%) patients were 80 years or older. Of patients undergoing clipping of unruptured intracranial aneurysms, 11081 patients (37.1%) were younger than 50 years old, 13479 patients (45.1%) were between 50 and 64 years old, 5186 (17.4%) were between 65 and 79 years old, and 140 (0.5%) patients were aged 80 years or older. In both the clipping and coiling groups, older patients had more comorbidities when compared to younger patients (P<0.0001 in both groups). For patients younger than 50 years, 50 to 64 years, and 65 to 79 years, clipped patients generally had less comorbidities than clipped patients (P<0.0001 for both groups). For patients 80 years or older, there was no significant difference between the average number of comorbidities between clipped and coiled patients (P=0.16).

Outcomes: Discharge Status, Mortality, and Length of Stay
Outcomes data are summarized in Tables 1, 2, 3, and 4 and in the Figure. For both clipped and coiled patients, increasing age was associated with increasing rates of discharge to...
Table 3. Outcomes for Patients 65 to 79 Years Old

<table>
<thead>
<tr>
<th>Discharge status</th>
<th>Clipped</th>
<th>Coiled</th>
<th>χ²</th>
<th>Risk Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home, N (%)</td>
<td>3645 (70.3)</td>
<td>8380 (91.3)</td>
<td>&lt;0.0001</td>
<td>0.77 (0.76–0.78)</td>
</tr>
<tr>
<td>Short-term facility, N (%)</td>
<td>39 (0.8)</td>
<td>79 (0.9)</td>
<td>0.02</td>
<td>0.87 (0.60–1.28)</td>
</tr>
<tr>
<td>Alive but unknown, N (%)</td>
<td>10 (0.2)</td>
<td>10 (0.1)</td>
<td>0.14</td>
<td>1.77 (0.74–4.25)</td>
</tr>
<tr>
<td>Long-term facility, N (%)</td>
<td>1390 (26.8)</td>
<td>636 (6.9)</td>
<td>&lt;0.0001</td>
<td>3.87 (3.54–4.22)</td>
</tr>
<tr>
<td>In-hospital death, N (%)</td>
<td>102 (2.0)</td>
<td>73 (0.8)</td>
<td>&lt;0.0001</td>
<td>2.47 (1.83–3.33)</td>
</tr>
<tr>
<td>Mean LOS (SD)</td>
<td>8.3 (19.4)</td>
<td>3.4 (11.5)</td>
<td>&lt;0.0001</td>
<td>...</td>
</tr>
<tr>
<td>No. of comorbidities, mean (SD)</td>
<td>1.6 (2.5)</td>
<td>1.4 (2.4)</td>
<td>&lt;0.0001</td>
<td>...</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LOS, length of stay; SD, standard deviation.

Table 4. Outcomes for Patients 80 Years or Older

<table>
<thead>
<tr>
<th>Discharge status</th>
<th>Clipped</th>
<th>Coiled</th>
<th>χ²</th>
<th>Risk Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home, N (%)</td>
<td>63 (45.0)</td>
<td>663 (82.0)</td>
<td>&lt;0.0001</td>
<td>0.55 (0.46–0.66)</td>
</tr>
<tr>
<td>Short-term facility, N (%)</td>
<td>0 (0.0)</td>
<td>14 (1.7)</td>
<td>0.24</td>
<td>0*</td>
</tr>
<tr>
<td>Alive but unknown, N (%)</td>
<td>0 (0.0)</td>
<td>5 (0.6)</td>
<td>0.55</td>
<td>0*</td>
</tr>
<tr>
<td>Long-term facility, N (%)</td>
<td>47 (33.5)</td>
<td>79 (9.8)</td>
<td>&lt;0.0001</td>
<td>3.44 (2.51–4.70)</td>
</tr>
<tr>
<td>In-hospital death, N (%)</td>
<td>30 (21.4)</td>
<td>20 (2.4)</td>
<td>&lt;0.0001</td>
<td>8.67 (5.07–14.82)</td>
</tr>
<tr>
<td>Mean LOS (SD)</td>
<td>12.7 (23.0)</td>
<td>4.8 (13.5)</td>
<td>&lt;0.0001</td>
<td>...</td>
</tr>
<tr>
<td>No. of comorbidities, mean (SD)</td>
<td>1.8 (2.0)</td>
<td>1.6 (2.5)</td>
<td>0.16</td>
<td>...</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LOS, length of stay; SD, standard deviation. *95% CI or relative risk could not be calculated because of 0 value in clipped group.

long-term facility (P<0.0001 for both clipped and coiled groups) and in-hospital mortality (P<0.0001 for both clipped and coiled groups). Mean length of stay also increased significantly with increasing age in both groups (P<0.0001 for both clipped and coiled groups).

Patients younger than 50 years old undergoing clipping of unruptured aneurysms had a discharge to long-term facility rate of 8.1% (526/11 081) compared to 3.5% (352/10 195) for coiled patients (Table 1). This difference was found to be statistically significant (P<0.0001). When comparing in-hospital mortality, no significant difference was detected as 0.6% of clipped patients (60/11 081) and 0.6% of coiled patients (59/10 195) experienced in-hospital mortality (P=0.72). Patients undergoing coiling had a significantly shorter mean length of stay (3.0 days; SD=9.4) when compared to patients undergoing clipping (6.1 days; SD=13.2; P<0.0001).

Patients 50 to 64 years old undergoing clipping of unruptured aneurysms had a discharge to long-term facility rate of 13.7% (1849/13 479) compared to 4.0% (560/13 862) for coiled patients (Table 2). This difference was found to be statistically significant (P<0.0001). When comparing in-hospital mortality, a significant difference was also noted with mortality rates of 1.1% (153/13 479) in clipped patients and 0.5% (68/13 862) in coiled patients (P<0.0001). Patients between 50 and 64 years old undergoing coiling had a mean hospital length of stay of 3.0 (SD, 9.2) days versus 6.6 (SD, 13.9) days in the clipping group (P<0.0001).

For patients 65 to 79 years old (Table 3), clipping was associated with a decreased rate of discharge to long-term facility when compared to clipping as 6.9% (636/9178) of coiled patients and 26.8% (1390/5186) of clipped patients were discharged to long-term facilities (P<0.0001). In-hospital mortality rate in this age group was 0.8% (73/9178) in coiled patients and 2.0% (102/5186) in clipped patients (P<0.0001). Length of stay was also significantly shorter for coiled patients; mean length of stay was 3.4 (SD, 11.5) days for coiled patients and 8.3 (SD, 19.4) days for clipped patients (P<0.0001).

Patients 80 years and older (Table 4), coiled patients had decreased rates of discharge to long-term facilities; 9.8% (79/809) of coiled patients and 33.5% (47/140) of clipped patients were discharged to long-term facilities (P<0.0001). The mortality rate for coiled patients was 2.4% (20/809) compared to 21.4% (30/140) for clipped patients (P<0.0001). The mean length of stay was 4.8 (SD, 13.5) days for coiled patients compared to 12.7 (SD, 23.0) days for clipped patients (P<0.0001).

Multivariate Results

When performing multivariate logistic regression analysis, we found that increasing age, clipping procedures, male gender, and non-white race were the only statistically significant predictors of discharge to a long-term facility (P<0.0001 for all 4 variables). No comorbidities were associated with discharge to a long-term facility and neither was the sum of comorbidities (P=1.00 for all comorbidities and sum of comorbidities). When studying predictors of mortality, we found that increasing age (P<0.0001), male gender (P=0.01), clipping procedures (P<0.0001), and non-white race (P=0.0007) were associated with increased mortality rates. Again, no comorbidities or sum of comorbidities were associated with an increased risk of mortality (P=1.00 for all comorbidities and sum of comorbidities).

Discussion

In this study, we found that improvements in short-term outcome with endovascular coiling relative to surgical clipping are amplified in elderly patients. Patients 65 years and older who underwent clipping of intracranial aneurysms had a mortality rate of 2.5% compared to only 0.9% for patients undergoing coiling. The difference in the discharge to long-term facility rate was also marked, occurring in 27.0% of patients undergoing clipping compared to only 7.4% for inpatients undergoing coiling. These differences in outcomes were even more pronounced for patients 80 and older when...
compared to their younger counterparts. In this age group, the mortality rate was nearly 10-times higher among clipped patients. In addition, one-third of patients 80 years or older were discharged to long-term facilities compared to <10% of coiled patients of similar age. As expected, younger patients undergoing both clipping and coiling had significantly better outcomes than their older counterparts.

There are only a few case series examining outcomes of coiling of unruptured aneurysms in the elderly. In a study by Gonzalez et al., 97 elderly patients (70 years and older) with 103 unruptured intracranial aneurysms underwent endovascular embolization. Of these patients, 88 (91.0%) had a good outcome (modified Rankin scale score 2), the rate of procedure-related death was 0.0%, and the rate of new neurological deficits was 6.0%. In a study by Cai et al., 22 patients aged 70 years or older with symptomatic unruptured aneurysms underwent endovascular embolization. Of these 22 patients, 1 (5.0%) had a modified Rankin scale score of 2 to 3 and 1 patient died (5.0%). Barker et al.1 used the NIS to examine outcomes of treating elderly patients with unruptured intracranial aneurysms between the years 1996 and 2000. They demonstrated that for patients 65 years of age and older, both discharge disposition and mortality were significantly better for patients undergoing endovascular coilng when compared to patients undergoing surgical clipping, but that the difference in discharge disposition was attributable to differences in discharge rates to short-term care facilities.1 Perhaps differences in outcomes between that study and ours can be accounted for because only 421 cases of coiling were included in that study, and data were collected relatively early in the era of endovascular aneurysm therapy. Our study, including treated patients from 2001 to 2008, gives an assessment of endovascular therapy more relevant to current practice.

Although a number of retrospective studies have demonstrated the feasibility of endovascular treatment for ruptured aneurysms in the elderly, the best evidence comes from the International Subarachnoid Aneurysm Trial. In a subgroup analysis of the International Subarachnoid Aneurysm Trial of 278 elderly patients with subarachnoid hemorrhage, 39.9% of patients with subarachnoid hemorrhage treated with endovascular therapy were dependent or dead at 1 year, compared with 43.9% in the surgical group.2 In patients with internal carotid artery or posterior communicating artery aneurysms, 72.0% of patients undergoing endovascular therapy were independent compared to only 52.0% undergoing clipping.2 However, the reverse was true for middle cerebral artery aneurysms because clipping was found to result in better outcomes than coiling. It is not unreasonable to expect that the overall benefit with endovascular therapy International Subarachnoid Aneurysm Trial shown in elderly patients with subarachnoid hemorrhage also would be seen in patients with unruptured cerebral aneurysms. It is therefore, perhaps, not surprising that this benefit is reflected in the NIS database.

These findings are an important contribution to the ongoing debate regarding treatment of unruptured aneurysms. Although there is much evidence to suggest that conservative management of unruptured aneurysms is a reasonable alternative to surgical or endovascular treatment, many still pursue the treatment of both asymptomatic and symptomatic unruptured intracranial aneurysms, even in the elderly. Overall, there appears to be a nationwide trend to treat elderly patients in the least invasive manner. Between 2001 and 2008, 65% of patients in the NIS older than age 65 years and 85% of patients older than age 80 years were treated with endovascular coiling rather than surgical clipping. Conversely, for younger patients the rates of coiling and clipping were much more equally distributed. In the event that treatment is considered and the aneurysm is considered to be amenable to safe endovascular treatment, the data from this study suggest that elderly patients should generally undergo endovascular coiling as the outcomes in both length of hospital stay, discharge to long-term facility, and mortality are remarkably superior to those seen after surgical clipping. In cases of elderly patients in which aneurysms underwent clipping, it is entirely possible that physicians felt that clipping was the best option because of risk of rupture, treatment availability, aneurysm location and geometry, and
presence of other vessel disease. However, these data suggest that it is highly questionable whether surgery should be performed at all compared to no treatment if clipping is not an option. The NIS database does not allow for assessments of particular aneurysm locations, so it might be true that the outcome advantage of clipping therapy does not hold true for all aneurysm locations, as noted in International Subarachnoid Aneurysm Trial.2

Certainly, there are instances in which endovascular coiling may not be a feasible option or may not be preferable, but in these cases one must carefully weigh the higher periprocedural rates of morbidity and mortality associated with clipping versus the risk of rupture of the unruptured aneurysm. Whereas the mortality rate from surgical clipping for patients 65 years and younger is 0.9%, the mortality rate for patients 80 years and older is 21.4%, likely much greater than the risk of dying from most untreated unruptured aneurysms.

This study has a number of limitations. We acknowledge that some coding inaccuracies undoubtedly occur that can affect the retrospective evaluation of an administrative database. This potential limitation is no different than in other studies of cerebral aneurysms using such databases.10 Additionally, we are unable to elucidate the symptomatic status of these treated unruptured aneurysms. Symptomatic unruptured aneurysms are at an increased risk for bleeding and, in these cases, treatment is certainly warranted and may result in increased complication rates. Overall, symptomatic aneurysms are a minority of unruptured aneurysms but they represent approximately three-quarters of aneurysms that bleed on follow-up. Also, this database does not offer any data on aneurysm geometric features (aspect and dome-to-neck ratio), size, location, presence of intracranial atherosclerosis, or presence of proximal vessel occlusion.

Long-term outcomes cannot be measured in the NIS, but it is reasonable to assume that discharge status has a significant correlation with long-term outcome. For example, in International Study of Unruptured Intracranial Aneurysms,11 30-day morbidity and mortality were 13.7% with surgery and 9.3% with endovascular therapy, whereas at 1 year they were 12.6% and 9.8%, respectively. It might also be argued that the higher recurrence rate associated with clipping compared to coiling could lead to hemorrhages that negate some of the better periprocedural outcome. International Subarachnoid Aneurysm Trial and Cerebral Aneurysm Rerupture After Treatment showed that the risk of recurrent hemorrhage of ruptured aneurysms after clipping was only slightly increased after coiling compared with clipping, and it is reasonable to expect that clipping would offer a similar relative efficacy for preventing hemorrhage from unruptured aneurysms. In comparing long-term outcomes for unruptured aneurysms treated with clipping versus coiling, small differences in hemorrhage rates over the years are unlikely to overcome the relatively large differences in periprocedural morbidity and mortality, especially among elderly patients.

Our study is retrospective and patients were not treated in a randomized manner. Therefore, there is significant potential for selection bias that might affect outcomes of clipping or coiling. We found that, generally, patients undergoing clip-

Conclusions

Although limitations exist, the NIS provides interesting and useful data regarding outcomes of patients treated across the United States for unruptured cerebral aneurysm. The NIS probably offers a more accurate “real world” perspective than single-center retrospective studies. Based on our findings, we think it is reasonable to conclude that older patients who undergo treatment of unruptured cerebral aneurysms generally tend to have significantly less morbidity and mortality with endovascular coiling than with surgical clipping.

Disclosures

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未破裂脳動脈瘤の治療の転帰に対する年齢の影響
— 2001 〜 2008 年 National Inpatient Sample の研究

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Abstract

背景および目的: 未破裂脳動脈瘤の治療として外科的クリッピングを受けた患者と血管内コイル療法を受けた患者では、年齢が転帰に及ぼす影響が異なる可能性がある。我々は大規模な公的データベースを評価し、未破裂脳動脈瘤の治療を受けた患者の年齢が転帰に及ぼす影響を明らかにした。

方法: National Inpatient Sample を用いて、2001年から2008年までに米国で未破裂脳動脈瘤のクリッピングまたはコイルリングを受けた患者注)の罹病率（長期施設への転院）および死亡率を評価した。転帰を50歳未満、50〜64歳、65〜79歳、80歳以上の4つの年齢層に分けて評価した。

結果: 50歳未満のコイルリングを受けた患者では、クリッピング受けた患者と比べて罹病率（3.5% 対 8.1%, p < 0.0001）、死亡率（0.6% 対 0.6%, p = 0.72）が低かった。50〜64歳のコイルリングを受けた患者では、クリッピング受けた患者と比べて罹病率（4.0% 対 13.7%, p < 0.0001）、死亡率（0.5% 対 1.1%, p < 0.0001）が有意に低かった。65〜79歳のコイルリングを受けた患者では、クリッピングを受けた患者と比べて罹病率（6.9% 対 26.8%, p < 0.0001）、死亡率（0.8% 対 2.0%, p < 0.0001）が低かった。80歳以上のコイルリングを受けた患者の場合は、クリッピングを受けた患者と比べて罹病率（9.8% 対 33.5%, p < 0.0001）、死亡率（2.4% 対 21.4%, p < 0.0001）が低かった。

結論: 血管内コイルリングによる治療を受けた患者は外科的クリッピングによる治療を受けた患者と比べて罹病率および死亡率が有意に低く、これらの差は年齢の増加とともにより明白になる。

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図 年齢群別にみたクリッピングとコイルリングの罹病率および死亡率。

注: 本研究に用いられた症例数はコイルリング 34,054 例、クリッピング 29,886 例である。