

Treatment Options of Unruptured Intracranial Aneurysms

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Aneurysmal subarachnoid hemorrhage (SAH), despite improvements in surgical and medical treatment, is still a serious disease with high rates of case fatality (40% to 50%) and morbidity.¹⁻³ Incidence rates of SAH have not changed during the CT era, and outcome of SAH has only modestly improved during the past few decades. Outcome is still determined mainly by severity of initial bleeding or early rebleeding.¹⁻⁴ It seems that identification of preventive treatment methods for aneurysm rupture and of modifiable risk factors for SAH are important as means to influence incidence and outcome of this serious disease.

Unruptured aneurysms, when incidentally discovered or found in connection with diagnosis of ruptured aneurysm (multiple aneurysm cases), have been operated on for 2 to 3 decades in western countries. In this way, the high case fatality and morbidity associated with a possible severe initial bleed can be eliminated by preventive surgical intervention. However, the natural history as well as risks of surgery of unruptured intracranial aneurysms are poorly known as are the risk factors for rupture because of lack of studies with sufficient number of patients and follow-up years.

The Table shows cohorts of largest studies of rupture risk of unruptured intracranial aneurysms.⁴⁻⁸ The recently published prospective part of The International Study of Unruptured Intracranial Aneurysms (ISUIA; patient enrollment in 61 centers between 1991 and 1998)⁵ shows somewhat different results as compared with those of the retrospective part of ISUIA (in 53 centers between 1970 and 1991).⁷ In the prospective study,⁵ overall incidence of aneurysm rupture was higher (0.8% versus 0.3% per year); risk for rupture of vertebrobasilar aneurysms was lower (relative risk 2.3 versus 5.1 to 13.8 as compared with other aneurysms); mean follow-up time per patient was shorter (3.9 versus 8.3 years); there was a lower limit of aneurysm diameter for very low risk for rupture in patients without a prior SAH (<7 versus <10 mm); and there was a nonsignificant direct association between patient age and aneurysm rupture risk as compared with the results obtained in the retrospective study.⁷ Although the ISUIA included a large number of patients, it has some important sources of bias as was suggested by differences between results of prospective and retrospective studies, for which reason the results may be difficult to generalize to

patient populations with unruptured aneurysms, and the results should be noted with some caution. In addition, among adults aged >30 years, annual incidence rates of SAH are at least 30 to 40 per 100 000. Estimated aneurysm prevalence rates for adults are 2% to 5%.^{1,3,8} Thus, expected rupture incidence of unruptured aneurysms in the general adult population is at least 1% per year, which does not sufficiently support the results of ISUIA. Rupture risks reported by the ISUIA may be somewhat underestimated, which is also suggested by the fact that the majority of the ruptured aneurysm are <10 mm in diameter.

Patients of the ISUIA were collected from the time period when unruptured intracranial aneurysms have been operated on to a great extent, particularly in patients of working age, as can be seen in the proportion of patients (58%) who were operated on with either open or endovascular surgery.⁵ In both parts of the ISUIA, the follow-up study included only a selected proportion of patients with unruptured aneurysms, and the number of patients who were excluded remained unknown. Centers participating in the ISUIA should have seen considerably more eligible patients than were included in the study (≈ 10 patients per center per year in the prospective and ≈ 1 patient per center per year in the retrospective study). Furthermore, patients whose unruptured aneurysms were operated on were younger and significantly ($P < 0.01$) more likely to be current cigarette smokers than those with no surgery.⁵ Patients, excluded for several reasons from the retrospective study, were also more likely younger and cigarette smokers than those who were included since cigarette smoking is more prevalent among young people,^{6,7,9-11} and because cigarette smokers more likely to refuse to take part in studies than nonsmokers.⁹ These patients excluded from the natural history study of the ISUIA may have had aneurysms that would have been more susceptible to growth and rupture.^{6,12}

The results of the natural history study of unruptured aneurysms from the Helsinki University Central Hospital (patient enrollment in 1 center between 1956 and 1978)^{4,6,8} have been reported several times since 1960 as the number of patients and follow-up years increased with elapsed time.¹³ This cohort had a long-term follow-up (mean 18.2, median 19.7 years per patient), had no surgical selection, and had a complete follow-up of cases with unruptured aneurysms, but the number of patients was modest as compared with that of ISUIA, and almost all were patients of working age and had multiple aneurysms with the ruptured aneurysm clipped at the start of follow-up.^{4,6} So, these results cannot necessarily be generalized to those patients with advanced age who have incidentally found aneurysms. These kind of cases are increasingly found on either magnetic resonance angiography or 3-dimensional CT angiography. On the other hand, the annual rupture rate of 1.3% (95% confidence interval, 0.9%

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Risk of Rupture of Unruptured Intracranial Aneurysm

Study	No. of Patients	No. of SAHs	Follow-Up, y	Incidents per Year, %	Risk Factors	References
ISUIA 2003	1692	51	6544	0.8	1, 2, 3	5
Juvela 2000, 2003	142	34	2577	1.3	1, 4, 5	4, 6
ISUIA 1998	1449	32	12023	0.3	1, 2, 3, 5	7
Juvela 1993	142	27	1944	1.4	1, (5)	8

ISUIA indicates International Study of Unruptured Intracranial Aneurysms.

1=aneurysm diameter, 2=aneurysm location, 3=aneurysm group (cases with previous SAH as compared with those without SAH), 4=cigarette smoking, 5=patient age.

to 1.7%) was similar to that of smaller previously published patient series (1% to 3%) and remained almost constant for decades. Significant risk factors for aneurysm rupture were cigarette smoking (tested as a time-dependent covariate), aneurysm diameter (linear association without any definite limit for very low risk rupture), and age, inversely.⁶ High systolic blood pressure values and long-term hypertension during follow-up predicted fatal aneurysm rupture.⁴ In addition, angiographic follow-up suggested that cigarette smoking, and possibly also female sex and patient age, inversely, hasten growth of preexisting aneurysm, making them prone to rupture.¹² In concordance with previous risk factor studies of multiple intracranial aneurysms, female sex and cigarette smoking were reported to increase risk for de novo aneurysm formation.¹² Although patients with multiple aneurysms have an increased risk for aneurysm formation, they do not have increased risk for rupture of unruptured aneurysm as compared with those with a single unruptured aneurysm.⁵⁻⁸

When deciding means of treatment of unruptured aneurysm, one must take into account not only maximum diameter of aneurysm^{5,6} but also patient age,⁶ location of aneurysm,⁵ history of hypertension⁴ and previous SAH⁵ as well as cigarette smoking.⁶ Indisputable modifiable risk factors for SAH are cigarette smoking, alcohol consumption, and hypertension.⁹⁻¹¹

In the prospective part of the ISUIA, risks of treatment were similar in open surgical and endovascular treatment groups.⁵ On the other hand, patients treated with endovascular coiling procedures were those who also had higher risks for poor outcome after operative treatment (older age, larger aneurysms, more often basilar tip aneurysms). However, aneurysmal obliteration was complete in only 51% of cases, and durability of treatment remained unknown due to a short follow-up time. Although endovascular coiling has been shown to be effective in prevention of rebleeding after aneurysmal SAH,¹⁴ its use for treatment of unruptured aneurysms is questionable since benefit of treatment cannot be seen until a follow-up of several decades. Particularly incomplete coiling of large aneurysms (failures of organization of intra-aneurysm thrombus, complete fibrous aneurysm obliteration, and endothelialization of aneurysm orifice) can lead to a recanalization and unexpected growth and rupture of aneurysm during follow-up,¹⁵ and these aneurysms are difficult to treat later with open surgery. However, coiling of unruptured aneurysms may be useful in an older patient with a basilar tip aneurysm, which is not large (<12 mm) and has a narrow neck.^{5,15}

Risks of open surgery of unruptured aneurysms of the ISUIA (mortality 1.5% to 2.3%, disability 10% to 12%)⁵ were similar to those obtained in a recent meta-analysis (overall mortality 2.6%, permanent disability 10.9%).¹⁶ In the latter study, technically difficult aneurysms were overrepresented (giant aneurysms ≥ 25 mm] 27%, posterior circulation aneurysms 30%).¹⁶ Thus, these favorable results were likely affected by publication bias. Authors calculated the following unfavorable results for specific aneurysm groups: anterior nongiant aneurysms, mortality 0.8% and morbidity 1.9%; posterior nongiant aneurysms, 3.0% and 12.9%; anterior giant aneurysms, 7.4% and 26.9%; and posterior giant aneurysms, 9.6% and 37.9%, respectively.¹⁶

As estimated from the above-mentioned studies, operative treatment should be considered for all unruptured aneurysms in patients aged <50 to 60 years (open surgery) as well as perhaps for aneurysms of ≥ 7 mm in diameter in older patients (open surgery or endovascular treatment) if there are no contraindications and patients have no serious preexisting diseases.^{5,6} Patients with symptomatic aneurysms should be candidates for operative treatment irrespective of age since symptoms may be due to a minor leak or growing aneurysm that predict a major rupture. Open surgery is a preferable method for treatment, but coiling of unruptured aneurysms may be a good alternative in elderly patients and in those with a basilar tip aneurysm, if the aneurysm is not large (<12 mm) and has a narrow neck.^{5,15} Final techniques of treatment of unruptured aneurysms depend on the experience of neurosurgeons and neuroradiologists of each center. Finally, cessation of cigarette smoking and active treatment of hypertension are important for the patients with unruptured aneurysms irrespective of methods of treatment of these lesions.^{4,6,9-12}

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