Taiwan Aneurysm Registry: Multivariate Analysis of Two-Month, One-Year, and Two-Year Outcomes after Endovascular and Microsurgical Treatment of Ruptured Aneurysms

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Summary

We compared the outcomes of endovascular coiling with microsurgical clipping of aneurysms in a Taiwanese population.

In an ambi-directional cohort design, patient baseline characteristics and clinical course after treatment for ruptured subarachnoid aneurysm were abstracted from medical records from three hospitals to examine and compare differences in post-operative outcomes between those treated with endovascular coiling and those treated with microsurgical clipping. Outcomes were measured, using the modified Rankin scale, two months, one year and two years postoperatively.

Of the 642 patients enrolled in the study, 281 underwent endovascular treatment and 361 underwent neurosurgery. The demographics and baseline characteristics of two groups were comparable except for a larger maximum target aneurysm lumen size ($p=0.02$) in the endovascular group. Patients who underwent the endovascular procedure tended to have a better quality of life than those who had neurosurgery ($p<0.01$). When the severity of symptom data was pooled into two groups (Rankin values 0-2 and 3-6) a statistically significant relationship was found between the severity of symptoms and age, Hunt and Hess grade, number of target aneurysms detected, and log of maximum target aneurysm lumen size (all $p\leq0.01$). After controlling for potential confounding factors and using the lumped Rankin outcome data, no significant difference in outcome was found between the two procedures at either time point.

Our study indicated that endovascular coiling achieves results comparable to surgical clipping for patients with ruptured subarachnoid aneurysms in a Taiwanese population.

Introduction

In response to the results of the landmark, large, randomized international subarachnoid aneurysm trial (ISAT), the management of cerebral aneurysms by microsurgical clipping has increasingly been replaced by the alternate procedure, endovascular coiling, a procedure that in the ISAT data showed a 23.9% relative risk reduction for dependency or death, and an absolute risk reduction of 7.4% over microsurgery [1]. Questions from this study about long-term outcomes and the risk of re-bleeding after clipping or coiling [2-4] were answered in a follow-up ISAT report (ISAT-2) and in the cerebral aneurysm rerupture after treatment (CARAT) study [5]. Late re-rupture occurred more frequently after coil-embolization than after clipping, but complication rates were similarly low in both procedures.

A prospective, randomized trial to obtain clear statistical results uses a carefully defined population in order to eliminate the effect of bias and random statistical 'noise' on the results. One question about such a trial is always to what degree the results on the selected population apply to the unselected, larger population. The question of to what degree the ISAT results are applicable to the general cerebral ruptured aneurysm patient population [6,7] has not yet been thoroughly investigated. Results of different studies vary, and the impact of confounding factors on these results has not been thoroughly addressed. Because of this uncertainty, we attempted to examine the differences in outcome between the use of endovascular coiling and surgical clipping for repair of aneurysm after hemorrhage in a Taiwanese population using multifactorial analysis and an ambidirectional cohort design (retrospective chart review and prospective follow-up data collection).

Materials and Methods

Study design

This ambidirectional cohort design utilized a retrospective chart review to identify patients and prospective follow-up data collection after the patients were identified. Multivariate logistic analysis of the data was used to remove the influence of confounding factors on comparison between the two treatments.

Patients

From January 2001 to December 2005, 642 patients were recruited in this study. The hospitals selected each had at least one neurosurgeon and one neurointerventionalist, each of whom had had a minimum of five years experience in cerebrovascular treatment. The cases reviewed were all ruptured intracranial aneurysms, and comprised approximately two thirds of the total ruptured intracranial aneurysm cases in the Taiwanese population during this time period.

Patient eligibility was contingent upon the following factors: 1) patient presented with a definite subarachnoid haemorrhage, substantiated by computed tomography (CT) or lumbar puncture, 2) patient exhibited an intracranial aneurysm, substantiated by conventional or CT angiography, which was responsible for the recent subarachnoid hemorrhage; 3) informed consent was obtained after a) an explanation by a neurosurgeon of the patient's condition, b) a presentation of treatment alternatives along with their respective advantages and disadvantages, and c) the patient, or a first degree relative if the patient had a high Hunt and Hess grade, had made a competent, autonomous decision on the treatment modality to be used; and 4) patients were in a clinical state, throughout the course of this study, for which either neurosurgical or endovascular treatment was justified. The final decision as to which treatment to be used was, in each case, made by the patient or the first degree relative, after being informed of the advantages and disadvantages of each treatment. The patients were referred for endovascular treatment by the neurosurgeons if coiling was the final decision.

Exclusion criteria were the following: 1) no clip or coil was placed; 2) consent was refused; 3) patient was participating in another randomized clinical trial of treatment for subarachnoid hemorrhage; (4) no treatment; (5) no follow-up; and (6) those with an unruptured aneurysm or dissecting aneurysms. The human subject review boards and ethics committees at each participating institution approved all aspects of this study.

Procedures

Patient baseline characteristics, treatment selected, and post-treatment clinical outcome were abstracted from medical records. A minimization algorithm, based on age, sex, clinical grade on the Hunt and Hess grading system, and size and location of the target aneurysm was applied in order to achieve statistical consistency.

Results were measured using the modified Rankin scale (0-6) – this parameter was assessed two months, one year and two years postoperatively, and annually thereafter. Data collection after the two month period was performed through follow-up clinical visits. For patients who did not return for follow-up, phone call reminders and phone questionnaires were

Table 1 **Demographics and baseline clinical characteristics of coiling and clipping.**

Variable	Coiling (n=281)	Clipping (n=361)	P-value[b]
Age (mean±SD)	55.60±15.21	56.90±13.36	0.26
Gender			0.10
Male	111 (39.5)	120 (33.2)	
Female	170 (60.5)	241 (66.8)	
H&H Grade [a]			0.10
Grade 1	156 (56.3)	171 (48.7)	
Grade 2	24 (8.7)	42 (12.0)	
Grade 3	14 (5.1)	24 (6.8)	
Grade 4	40 (14.4)	70 (20.0)	
Grade 5	43 (15.5)	44 (12.5)	
Number of target aneurysms detected			0.09
1	222 (80.4)	290 (80.8)	
2	42 (15.2)	63 (17.5)	
3	11 (4.0)	4 (1.1)	
4	1 (0.4)	1 (0.3)	
5	0 (0.0)	1 (0.3)	
Maximum target aneurysm lumen size (mm)			<0.01*
< 5	80 (31.0)	138 (42.1)	
≧ 5	178 (69.0)	190 (57.9)	

[a] *Hunt and Hess grading system*
[b] *The comparisons between two treatments were conducted by Student's t-test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables.*
**P<0.05, as shown a significant difference between the two groups.*

used. Those who were lost after abortive phone call attempts had been made were not included in the results. Routine follow-up studies consisted of diagnostic measures such as conventional angiography and MRA, procedures contingent upon patient consent. Diagnostic angiogram findings were then recorded on the follow-up forms.

Statistical methods

Data were expressed by means with standard deviations (SDs) for continuous variables and numbers with percentages for categorical variables. The difference in age between two treatments was conducted by Student's t test. Patient demographics and baseline clinical characteristics for the two treatment groups were compared using independent t-tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Association between outcomes and treatments was evaluated by the chi-square test, and univariate logistic regressions were fitted to explore the relationship between binary outcomes and risk factors. Finally, multivariate logistic regressions were constructed to examine the effect of the two therapies on binary outcomes after adjustment, based on the univariate analyses, for confounding factors. P-value<0.05 was considered to be statistically significant. SAS 9.1 (SAS Institute Inc, Cary, NC, USA) was used to perform all statistical analyses.

Results

Of the 642 patients enrolled in the study, 281 underwent endovascular treatment and 361 had neurosurgery. The demographics and baseline characteristics of the two groups (Table 1)

Table 2 **Association between procedures and outcomes (modified Rankin scale) at three time points.**

Outcome (modified Rankin scale)	2 months			1 year			2 year		
	Coiling (N=229)	Clipping (N=325)	P-value	Coiling (N=150)	Clipping (N=217)	P-value	Coiling (N=86)	Clipping (N=128)	P-value
0 No symptoms	89 (38.9)	77 (23.7)	<0.01*	77 (51.3)	58 (26.7)	<0.01*	48 (55.8)	58 (45.3)	0.39
1 Minor symptoms	54 (23.6)	102 (31.4)		29 (19.3)	70 (32.3)		19 (22.1)	31 (24.2)	
2 Some restriction on lifestyle	11 (4.8)	38 (11.7)		12 (8.0)	27 (12.4)		8 (9.3)	14 (10.9)	
3 Significant restriction on lifestyle	9 (3.9)	20 (6.2)		4 (2.7)	13 (6.0)		1 (1.2)	9 (7.0)	
4 Partly dependent	13 (5.7)	19 (5.9)		10 (6.7)	18 (8.3)		2 (2.3)	3 (2.3)	
5 Fully dependent	26 (11.4)	44 (13.5)		15 (10.0)	28 (12.9)		8 (9.3)	13 (10.2)	
6 Dead	27 (11.8)	25 (7.7)		3 (2.0)	3 (1.4)		–	–	

** Significantly associated between procedures and outcomes, Chi-square test.*

were comparable except for maximum target aneurysm lumen size, which was significantly larger (p<0.01) in the group that had endovascular coiling.

Thirty-two subjects for whom we had no clinical outcome data at two months and 56 patients who underwent both treatments were excluded from the analysis to prevent crossover effects. In addition, 187 patients who were lost to follow-up at the first year and the other 153 patients who were lost to follow-up at the second year were also excluded in the firstyear model and second year model respectively. The chi-square analysis of the seven level modified Rankin scale quality of life data (Table 2) showed that patients who had the endovascular procedure had a significantly better (p<0.01) quality of life than those who had microsurgery at both the two month and one year time period. But the association was not found in the second year time period (p=0.39).

Although the seven level modified Rankin scale data analysis showed endovascular treatment to result in a better quality of life than microsurgery, a second analysis of the data, taking confounding factors into account, gave a different result. In order to evaluate the effect of demographic factors and aneurysm type on the severity of symptoms after treatment, we sub-categorized the patients into two groups, modified Rankin scale ranks 0-2 and 3-6. Using a univariate analysis, the severity of post-treatment symptoms at the two month, one year, and two year follow-up was found to be significantly related to age, Hunt and Hess grade on admission (all p≤0.05, Table 3) in both group. The distribution of gender showed a significant relationship to outcome at one and two years. However, the relationship of target aneurysms detected and outcome showed a significant association at two months. When endovascular and microsurgical outcomes were then compared after controlling for the possible confounding factors discovered in the univariate analysis, there was no significant difference between the two procedures, with an odds ratio of =0.90 and a 95% confidence interval (0.57, 1.43) for the two months data; an odds ratio of 1.54 and a 95% confidence interval of (0.86-2.77) for the first year data; and an odds ratio of 3.51 and a 95% confidence interval (1.17, 10.55) for the second year data (all p-value>0.05, Table 4). However, people of older age or a higher Hunt and Hess grade had higher odds of reporting severe symptoms.

The aneurysms size was significantly different between the coiling and the clipping group (Table 1, p<0.01).

Table 3 **Univariate logistic regressions to identify possible factors at 2 months, 1 year and 2 years.**

Factors	2 months (N=554)			1 year (N=367)			2 years (N=214)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.04	1.02-1.05	<0.01*	1.04	1.02-1.06	<0.01*	1.05	1.02-1.09	<0.01*
Gender									
Male	Ref	–	–	Ref	–	–	Ref	–	–
Female	0.87	0.601.27	0.48	0.55	0.33-0.90	0.02*	0.33	0.15-0.71	<0.01*
H&H Grade									
Grade 1	Ref	–	–	Ref	–	–	Ref	–	–
Grade 2	2.36	1.16-4.78	0.02*	2.35	0.98-5.62	0.05	3.06	0.83-11.21	0.09
Grade 3	10.75	4.69-24.66	<0.01*	5.09	1.94-13.37	<0.01*	1.25	0.14-10.94	0.84
Grade 4	10.51	6.05-18.26	<0.01*	5.86	2.95-11.62	<0.01*	9.17	3.13-26.86	<0.01*
Grade 5	15.44	8.2029.07	<0.01*	9.06	4.09-20.05	<0.01*	13.75	4.27-44.3	<0.01*
Number of target aneurysm detected	1.50	1.04-2.15	0.03*	1.30	0.79-2.15	0.31	0.99	0.42-2.34	0.98
Max. target aneurysm lumen size									
< 5 mm	Ref	–	–	Ref	–	–	Ref	–	–
≧ 5 mm	1.49	1.01-2.20	0.05	1.63	0.96-2.76	0.07	2.39	0.93-6.15	0.07
Location									
Anterior cerebral artery	Ref	–	–	Ref	–	–	Ref	–	–
Internal carotid artery	0.83	0.54-1.27	0.39	0.96	0.54-1.70	0.88	0.70	0.29-1.69	0.43
Middle cerebral artery	0.80	0.45-1.43	0.45	1.05	0.52-2.15	0.89	1.04	0.37-2.90	0.94
Posterior circulation	0.84	0.44-1.61	0.60	0.70	0.28-1.78	0.45	0.19	0.02-1.55	0.12

* *Significantly related to dependency or death.*
H&H, *Hunt and Hess;* Max, *maximum;* Ref, *reference.*

Table 4 **Multivariate logistic regression to examine therapeutic effect on dependency or death (rank 3-6) at 2 months, 1 year and 2 years.**

Procedure	2 months (N=554)			1 year (N=367)			2 years (N=214)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Clipping	Ref	–	–	Ref	–	–	Ref	–	–
Coiling	0.93	0.59-1.47	0.76	1.55	0.86-2.78	0.14	3.54	1.17-10.69	0.02*

The two procedures were compared by multivariate logistic regression after adjustment of the possible factors significant in Table 3 and maximum target aneurysm lumen size that was significant in Table 1.
At 2 months, age, gender, H&H Grade and number of target aneurysm detected were included in the model for adjustment. At 1 year and 2 years, age, gender, and H&H Grade were included in the model for adjustment.
** Significantly related to dependency or death.*

Table 5 **Association between procedures and outcomes grouped by size at three time points.**

Outcome	2 months			1 year			2 years		
	Coiling	Clipping	P-value	Coiling	Clipping	P-value	Coiling	Clipping	P-value
Size ≦ 5 mm			0.99			0.31			0.48
Outcome < 3	63	113		52	78		31	50	
Outcome ≧ 3	25	45		10	23		2	7	
5 mm < Size ≦ 10 mm			0.57			0.21			0.40
Outcome < 3	63	74		47	54		33	38	
Outcome ≧ 3	31	43		14	26		6	11	
Size > 10 mm			0.43			0.33			0.66
Outcome < 3	17	13		11	10		6	8	
Outcome ≧ 3	12	14		5	9		2	5	

** Significantly associated between procedures and outcomes. The association between outcome and pro*

However, in the association between coiling and clipping and outcomes grouped by aneurysm size, there was no significant different between the two procedures at the three time points (Table 5).

Discussion

Clip/coil results vs. ISAT results

Although our univariate analysis of the data using all seven modified Rankin scale outcome categories showed a statistically significant superiority of endovascular treatment, our second, multivariate, analysis, using pooled modified Rankin scale and controlling for confounding variables, showed no significant difference in outcome between the two treatments.

By contrast, the ISAT trial, both in the first report and the follow-up report, showed a statistically significant superiority for endovascular treatment [1,5].

One difference between the two trials was in the selection of subjects. Our trial reported on actual on-going practice in our country, and treatment assignment was not random, but depended on the physician's judgment, biases, and experience and on patient preference. The ISAT trial, being a prospective, randomized trial, had patients with matching clinical characteristics in the two treatment arms and also, for ethical reasons, could only enter patients deemed equally likely to benefit from neurosurgical or endovascular treatment.

This difference in selection of subjects resulted in differences between the two populations. In the ISAT study, 50% of all aneurysms included in the study were anterior communicating aneurysms, 33% were in the internal carotid artery (mostly in the posterior communicating artery portion of this artery), and 14% were in the middle cerebral artery (an unsuitable location for coiling). These choices suggest that patients who were of "high surgical risks" [5,8] were under-represented compared to the general population. Our patient population was similar to that seen in actual practice, and so contained more than 35% high-risk (Hunt and Hess scores 3-5) patients, a much larger percentage than the 5 to 6% seen in the ISAT study. A recent retrospective comparison of microsurgical "clipping" and endovascular "coiling" in similar high-risk patients finds no difference in outcome between the two techniques in this patient population [9]. The ISAT data also shows that in older patients and in the few high risk patients they did enroll, that endovascular and microsurgical results were similar [5].

Microsurgery and good post-surgical quality of life

Microvascular surgery, being invasive, runs the risk of surgical injury (direct or indirect) to brain structures, and thus causing motor and cognitive effects in addition to those caused by the hemorrhage itself. Microsurgery patients might, therefore, have fewer "good" quality of life outcomes than endovascular patients even though the proportion with very poor outcomes, as in our sample, did not differ from that seen after endovascular "coiling." Our data suggests this to be true, for a significantly greater proportion of endovascular patients than microsurgical patients had "no symptoms" at two months, one year after treatment. This advantage is also seen in the ISAT data [1,5]. But the association was not found in the second year time period (p=0.39). We speculate this is due to more patients with mRs=0 in coiling group were lost to the two-year follow-up than in the clipping group.

Re-bleeding after endovascular "coiling"

Endovascularly placed coils do not always completely occlude the aneurysm, and the possibility of death or severe disability due to rebleeding, perhaps late after the original treatment, has been a concern. Our data does not permit an analysis of this question, but both the second ISAT report and the CARAT study report a very low rate of re-bleeding at late time periods [5,6].

Factors associated with poor post-treatment outcome

Our study, using univariate analysis of two treatment groups with almost identical demographics (with the exception of target aneurysm size), shows significant correlations between outcome and the following four parameters: severity of initial symptoms, age, log of maximum target aneurysm lumen size, and number of target aneurysms detected (all p≤0.01, Table 4).

Similar correlations have been reported by others. Chung et al. [10] reported that patients of older age (>70) and larger lumen diameter (>9 mm), had a poorer prognosis, a result confirmed by Sedat et al. [11] who showed more negative outcomes (GOS 3, 4, and 5) in older patients presenting with aneurysmal lumen diameters over 10 mm.

The ISUIA study [12] also indicated a correlation between surgery-related morbidity/mortality and age among 1172 patients with unruptured intracranial aneurysms.

Limitations

The limitations of this study that might have compromised the results were possible inconsistent neurosurgeon / neurointerventionalist experience; the qualifications and consistency of performance could not have been monitored or assessed prior to, or after, treatment. It should also be noted that this study is not randomized and that the patient distribution was skewed, and that the current assessment and results are derived only from a two-month, one-year, and two-year follow-up.

Conclusion

This study, which had a patient mix similar to that seen in practice, showed post-treatment outcome after subarachnoid aneurysm hemorrhage to be related to age, aneurysm lumen size, and severity of pre-treatment symptoms. When the data were adjusted for these confounding factors, surgical and endovascular treatments had similar success rates.

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