Factors affecting the durability of coil embolization for intracranial aneurysms

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Factors affecting the durability of coil embolization for intracranial aneurysms

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Young Sub Kwon

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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OBJECTIVE: Endovascular coil embolization for ruptured and unruptured intracranial aneurysms has proven to be safe and effective treatment modality. However, its long term durability still remains to be improved. This study aims to depict factors affecting the durability of coiled aneurysms by analysis of patient characteristics, aneurysm factors, and treatment outcome.

METHODS: Data for patients treated with endovascular coil occlusion in Yonsei university medical center between 2005 and 2009 were retrospectively reviewed. Patient and aneurysm characteristics, treatment outcome, and follow up results were collected and statistically analyzed to determine factors that affect in durability of coil embolization.

RESULTS: 228 aneurysms in 208 patients had adequate follow up data for evaluation of durability after coil embolization. 37 (16.2%) aneurysms recurred after an average of 19.5 months follow up. Patient factor associated with durability was treatment after rupture. Aneurysm factors such as size, depth, volume of aneurysm, aspect and bottleneck ratio were associated with durability. Treatment factors that were associated with durability were length of embolized coil, packing density, completeness of occlusion, and use of stent. Follow up duration and angiography as mode of follow up was also related to durability. Multivariate logistic regression identified volume of aneurysm, treatment after rupture, use of stent, and angiography as mode of follow up as significant predictors affecting durability after coil embolization.

CONCLUSION: The possible risk factors that affect the durability of coil embolization were larger aneurysm volume, treatment after rupture, and absence of stent remodeling. These factors may be considered for clinicians in case of deciding for coil embolization of intracranial aneurysms and long term follow up may be needed in presence of such risk factors.

Key words : coil embolization, intracranial aneurysms, durability, factors.

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I.INTRODUCTION

Intracranial aneurysms are found in approximately 1% of general population and rupture of intracranial aneurysm causing subarachnoid hemorrhage (SAH) occur with a yearly frequency of 6~8 per 100000.[1] The mortality rate of ruptured intracranial aneurysm reaches 25~50%, and about half of the survivors are left with permanent neurological deficit.[2] Although advances in microsurgical technique and devices significantly reduced the risk of surgery, introduction of endovascular technique in occlusion of intracranial aneurysm emerged as a powerful option in further reducing the risk.

Detachable platinum coil device was first introduced in 1990 as an investigational device to occlude aneurysm via endovascular route.[3] It was approved by US Food and Drugs Administration in 1995 and has become widely used in patients with ruptured and unruptured aneurysms.[4,5]

Recent developments in high-resolution imaging technology have increased the diagnosis of unruptured aneurysms, and respective roles of endovascular and surgical treatment remain to be proven.[6] Different options are offered to patients in different counties or institutions, and neurovascular team consisting of neurosurgeon, neurologist and radiologist may be needed in deciding the optimal treatment in complex lesions.[7] Endovascular treatment is less invasive in general, but its adequate long-term durability remains to be proven.[8-11]

International Subarachnoid Aneurysm Trial (ISAT) in 2002 suggested better outcome for endovascular treatment compared with neurosurgical clipping, but also demonstrated a significant higher rate of recurrence at follow up.[9,11] Although diversities in aneurysm characteristics and patient profiles obscure the true recurrence rate, numerous studies advocate the higher incidence of recanalization and recurrence after endovascular treatment.[11-15]

Many of the aneurysm characteristics such as location, different dimensions, and opening size have been analyzed in search for factors affecting durability of endovascular coiling. Larger aneurysm size and incomplete coil packing are frequently documented as factors that affect the durability.[12,15-17]

This study aims to further depict factors affecting the durability of coiled aneurysms through more detailed analysis of patient and aneurysm characteristics, treatment outcome and follow up radiologic results.

II. MATERIALS AND METHODS

From May 2005 to May 2009, 321 aneurysms in 299 patients were treated with endovascular coil embolization at Yonsei University College of Medicine. Of the 321 aneurysms, 228 aneurysms (71.0%) in 208 patients were included in this study that met the following criteria: 1) coil embolization was done as mode of occlusion, i.e. aneurysms that was treated with parent artery occlusion or stent only method was not included, 2) aneurysms that were not previously treated with either surgical or endovascular modality, 3) follow up duration of more than 3 months with evaluation for recurrence either with angiography or magnetic resonance angiography (MRA) as mode of radiologic evaluation. 93 (29.0%) aneurysms were lost to follow up, 5 (1.6%) aneurysms were treated with parent artery occlusion.

Patient data, aneurysm characteristics, and treatment and follow up radiologic results were retrospectively reviewed via Electronic Medical Record System and Picture Archive and Communications System files.

1) *Patient characteristics*

Patient characteristics such as sex, age, high blood pressure, and presence of concurrent aneurysm were collected.

2) *Aneurysm characteristics*

Aneurysm characteristics such as aneurysm length, width, depth, neck diameter, location, parent artery diameter, and aneurysm inflow angle were measured (*Fig.1*).

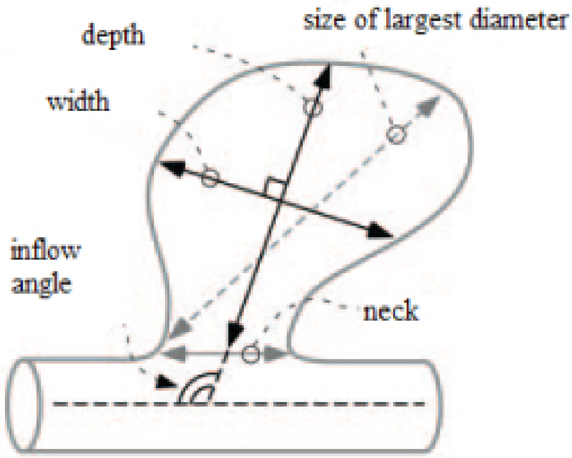

Figure 1. Schematic illustration of aneurysm dimensions

Aspect ratio (depth to neck ratio), bottleneck ratio (width to neck ratio), parent artery to neck ratio, and volume of aneurysm were calculated based on above measurements. Volume of aneurysm was calculated with the equation corresponding to volume of an scalene ellipsoid:

volume = $\frac{4}{3}\pi\left(\frac{\text{length}}{2}\right) * \left(\frac{\text{width}}{2}\right) * \left(\frac{\text{depth}}{2}\right)$. Locations of aneurysms were first classified according to its parent artery: internal carotid artery, anterior cerebral artery, middle cerebral artery, and vertebrobasilar system and latter classified according to branching type: side wall type, branching type, and bifurcation type (*Fig.2*).

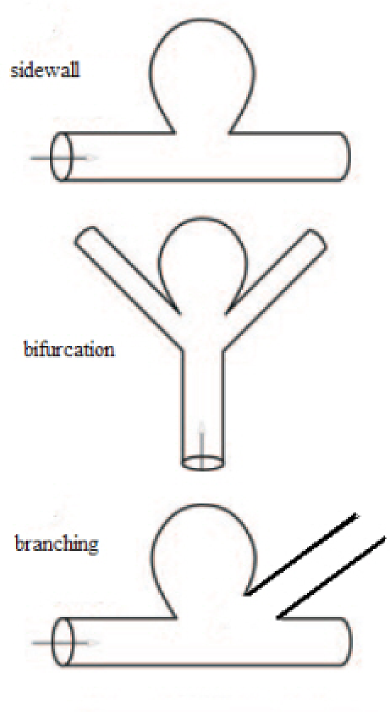

Figure 2. Schematic illustration of aneurysm classification according to branching type

3) *Treatment and follow up results*

Treatment results such as length of coil used, use of stent, and radiologic completeness of occlusion were analyzed. Volume of embolized coil was calculated with the equation: volume = $\pi\left(\frac{\text{coil diameter}}{2}\right)^2 * \text{length of coil used}$. Coil diameters are as published by Boston Scientific/Target (Fremont, CA), Cordis (Miami, Fl, USA) and ev3 (Plymouth, MN, USA). Initial radiologic completeness of occlusion was graded as complete, remnant neck, and incomplete (<80% occlusion). Packing density was calculated as following: packing density

$=\left(\frac{\text{embolized coil volume}}{\text{volume of aneurysm}}\right) * 100$. Follow up results were based on analysis of coil morphology, residual flow on conventional 2D and 3D angiography and magnetic resonance angiography.

4) *Statistical analysis*

Univariate analysis was done to evaluate association between each factors and recurrence. X^2 test and Fisher exact test were used for each factors and $P < 0.05$ was accepted as significant. Multivariate logistic regression analysis was performed for relevant factors and reported with 95% confidence intervals. All the data analyses were performed with PASW statistics version 18.0 (SPSS Inc., Somers, NY, USA).

III. RESULTS

Total of 228 aneurysms in 208 patients met the inclusion criteria. Of the 228 aneurysms, 37 (16.2%) aneurysms recurred. Mean follow up period was 19.5 months (range 4.3-54.6 months).

1. *Patient factors of stable and recurred coiled aneurysms*

Patient factors of stable and recurred coiled aneurysms are summarized in *Table 1*. Among the patient characteristics, treatment after rupture was the only potential factor that was statistically significant with recurrence.

Table 1. Patient factors of stable and recurred coiled aneurysms.

	Stable (%)	Recurred (%)	*P*
Sex			0.81
Male	37 (84.1%)	7 (15.9%)	
Female	138 (84.1%)	26 (15.9%)	
Mean age (years)	58.1	55.5	0.46
Hypertension			0.64
Yes	96 (86.5%)	15 (13.5%)	
No	79 (81.4%)	18 (18.6%)	
Treatment after rupture			0.026
Yes	28 (73.7%)	10 (26.3%)	
No	147 (86.5%)	23(13.5%)	
Concurrent aneurysm			0.55
Yes	62 (87.3%)	9 (12.7%)	
No	113 (82.5%)	24 (17.5%)	

2. Aneurysm factors of stable and recurred coiled aneurysms

Aneurysm factors of stable and recurred coiled aneurysms are summarized in *Table 2*. Univariate analysis identified size of largest diameter, depth, volume of aneurysm, aspect ratio, and bottleneck ratio as potential aneurysm factors related to recurrence.

Table 2.Aneurysm factors of stable and recurred coiled aneurysms.

	Stable (%)	Recurred (%)	***P***
Size of largest diameter			<0.0001
Small (<5 mm)	101 (94.4%)	6 (5.6%)	
Medium (5 ~ 10 mm)	77 (77.8%)	22 (22.2%)	
Large (10 ~ 25 mm)	12 (57.1%)	9 (42.9%)	
Giant (>25 mm)	1 (100%)	0 (0%)	
Depth			<0.0001
Shallow (<5 mm)	123 (93.2%)	9 (6.8%)	
Medium (5 ~ 10 mm)	61 (74.4%)	21 (25.6%)	
Deep (>10 mm)	7 (50.0%)	7 (50.0%)	
Neck size			0.54
Small (<3 mm)	75 (91.5%)	7 (8.5%)	
Medium (3 ~ 6 mm)	97 (80.2%)	24 (19.8%)	
Large (>6 mm)	19 (76.0%)	6 (24.0%)	
Volume of aneurysm			<0.0001
Small (<40 mm^3)	96 (96.0%)	4 (4.0%)	
Medium (40 ~ 120 mm^3)	52 (78.8%)	14 (21.2%)	
Large (>120 mm^3)	43 (69.4%)	19 (30.6%)	
Location as parent artery			0.113
Internal carotid artery	133 (85.3%)	23 (14.7%)	
Anterior cerebral artery	25 (89.3%)	3 (10.7%)	
Middle cerebral artery	5 (100.0%)	0 (0%)	
Vertebrobasilar system	28 (71.8%)	11 (28.2%)	

Location as branching type			0.60
sidewall	83 (86.5%)	13 (13.5%)	
branching	85 (85.9%)	14 (14.1%)	
bifurcation	23 (69.7%)	10 (30.3%)	
Aspect ratio			0.015
Very Broad (<1.2)	72 (92.3%)	6 (7.7%)	
Broad (1.20 ~ 1.8)	80 (82.5%)	17 (17.5%)	
Narrow (>1.8)	39 (73.6%)	14 (26.4%)	
Bottleneck ratio			0.020
Very broad (<1.2)	66 (90.4%)	7 (9.6%)	
Broad (1.2 ~ 1.8)	86 (85.1%)	15 (14.9%)	
Narrow (>1.8)	39 (72.2%)	15 (27.8%)	
Parent artery diameter			0.46
Thin (<2.8 mm)	49 (83.1%)	10 (16.9%)	
Medium (2.8 ~3.5 mm)	71 (80.7%)	17 (19.3%)	
Thick (>3.5 mm)	71 (87.7%)	10 (12.3%)	
Neck to parent artery ratio			0.21
Wide neck (>1.5)	48 (78.7%)	13 (21.3%)	
Medium (1.0 ~ 1.5)	63 (81.8%)	14 (18.2%)	
Thick parent artery (<1.0)	80 (88.9%)	10 (11.1%)	
Inflow angle			0.52
Acute (<110°)	97 (86.6%)	15 (13.4%)	
Intermediate (110~145°)	47 (81.0%)	11 (19.0%)	
Obtuse (>145°)	47 (81.0%)	11 (19.0%)	

3. Treatment outcome and follow up factors of stable and recurred aneurysms

Treatment outcome and follow up factors of stable and recurred aneurysms are summarized in *Table 3*. Treatment factors that were associated with recurrence were length of embolized coil, packing density, use of stent, and initial completeness of occlusion. Follow up duration and angiography as mode of follow up was also related to recurrence.

Table 3.Treatment outcome and follow up factors of stable and recurred coiled aneurysms

	Stable	Recurred	*P*
Length of embolized coil			<0.0001
Short (<20 cm)	85 (97.7%)	2 (2.3%)	
Intermediate (20 ~ 50cm)	55 (76.4%)	17 (23.6%)	
Long (>50 cm)	51 (73.9%)	18 (26.1%)	
Packing density			0.035
Very loose (<20%)	52 (74.3%)	18 (25.7%)	
Loose (20 ~ 30%)	77 (88.5%)	10 (11.5%)	
Dense (>30%)	62 (87.3%)	9 (12.7%)	
Use of stent			0.050
Yes	49 (92.5%)	4 (7.5%)	
No	142 (81.1%)	33 (18.9%)	
Initial completeness of occlusion			0.035
Complete	105 (84.7%)	19 (15.3%)	
Remnant neck	60 (89.6%)	7 (10.4%)	
Incomplete(<80% occlusion)	26 (70.3%)	11 (29.7%)	
Follow up duration			0.044
Less than 1 year	70 (90.9%)	7 (9.1%)	
2 years ~ 3 years	68 (84.0%)	13 (16.0%)	
More than 3 years	53 (75.7%)	17 (24.3%)	
Angiography as follow up			<0.0001
Yes	45 (62.5%)	27 (37.5%)	
No	146 (93.6%)	10 (6.4%)	

4. *Multivariate logistic regression*

Multivariate logistic regression identified volume of aneurysm, treatment after rupture, use of stent and angiography as mode of follow up as significant predictors of recurrence after coil embolization. Results of multivariate Analysis of risk factors for recurrence of coiled aneurysms are summarized in *Table 4*.

Table 4. Multivariate Analysis of risk factors for recurrence of coiled aneurysms

	OR	**95% Confidence Intervals**
Volume of aneurysm		
Small (<40 mm^3)⁎	**-**	**-**
Medium (40 ~ 120 mm^3)	8.89	2.62-30.16†
Large (>120 mm^3)	4.22	1.22-14.59†
Treatment after rupture		
No⁎	-	-
Yes	2.75	1.03-7.30†
Use of stent		
No	4.27	1.29-14.12†
Yes⁎	-	-
Angiography as follow up		
No⁎	-	-
Yes	7.52	3.14-18.01†

⁎Reference group

†Statistically significant value.

IV. DISCUSSION

Possible factors that affect the durability of coiled aneurysms are documented in many previous studies. Large aneurysm size and initial completeness of occlusion were frequently reported factors associated with durability.[18-20] In this study, similar results were observed while other factors also showed significant association with durability.

Although several studies reported treatment after rupture as a risk factor affecting durability, this finding was not consistent in other reports.[7,16,21] Nguyen et al[16] suggested possible mechanisms that may influence durability of coil embolization for ruptured aneurysms; presence of clot at aneurysmal dome, fear of aneurysm rerupture on procedure, partial extrusion of coil from aneurysm dome, or pathophysiology of ruptured aneurysm to halt aneurysm healing. However, in systematic review by Ferns et al[21] where completeness of occlusion did not differ for ruptured or unruptured aneurysms, the treatment after rupture did not affect the durability. Whether the irregular shape of ruptured aneurysms which hinder complete occlusion is the reason behind lower durability or other pathophysiology exists for ruptured aneuysms, more studies may be needed.

Size is a factor most studies uniformly report to affect durability, but aspect ratio and bottleneck ratio has not been widely investigated for its direct effect on durability. Some published the association of aspect ratio and bottleneck ratio to be factors related to occlusion outcome[22,23] and thus may be related to durability, the aneurysm morphology does have a trend in respect to its size. Many of the small aneurysms have wide neck while large aneurysms grow to have larger width or depth than its neck. This finding is supported by the significant association of bottleneck ratio to size in this study (X^2 test, P <0.001). The aspect and bottleneck ratio may have been influenced by the confounding factors (i.e. size or use of stent) and showed no significance on multivariate regression analysis. In fact, our observation of small broad neck aneurysms with larger aspect and bottleneck ratio had lesser recurrence than medium sized aneurysms with lesser aspect and bottleneck ratio.

Packing density and initial completeness of occlusion are factors some authors advocate to influence on durability.[24,25] In this study, packing density and initial completeness of occlusion were significant factors of recurrence in univariate analysis, but its statistical power was not enough to show significance in multivariate analysis. The relationship of packing density and initial completeness of occlusion showed significant association (P=0.009), but packing density was more strongly associated with size (P<0.0001), which might have influenced on the recurrence rate. One lack of analysis in this study was the types of coil (standard platinum or modified coil) used which might have influenced on recurrence independent of the packing density.

Location is a factor frequently searched by the clinicians for its relationship with recurrence rate.[21,26] However, the fact that surgical clipping always provide an alternative to coil embolization in surgery favorable locations, location factor is always under selection bias for its center to center differences in indications for surgery. Albeit with the selection bias, locations as parent artery failed to show meaningful statistical differences.

In this study, location was categorized further to type of arterial branching to see if the flow dynamics of the aneurysm affect the durability. Although statistically insignificant (*P*=0.60), bifurcation types as in internal carotid, middle cerebral and basilar bifurcation aneurysms showed highest recurrence rate owing to its greatest flow dynamic stress.

Kim et al reported that use of stent remodeling in coil embolization promote progressive thrombosis and lower the rate of recanalization.[27] Concordant result was observed as absence of stent as independent risk factor for recurrence with odds ratio as high as 4.27.

The problem with retrospective analysis lies on the selection bias which may grow with increasing heterogeneity of mode and interval of follow up. Number and rate of recurrences may vary upon the interval and mode of follow up.[7] This is confirmed by the result that follow up by mode of angiography was the independent risk factor for diagnosis of recurrence ($P<0.0001$) and increasing follow up angiography may actually increase rate of recurrences in our study. Although clinicians strongly recommend angiography for patients who have higher risk of recurrences, stable outcome on magnetic resonance angiography may not guarantee stable outcome for patients with lesser risk.

As for follow up intervals, majority of the patients were followed up with MRA after 6 months post-treatment and then angiography or MRA around 1 year and 2 years. The number of recurred patients increases at 12~18 months follow up and again at 24~30 months and over 30 months follow up($P = 0.044$)(*Fig.3*). This finding must be interpreted in relation to increase in follow up angiography done. Nonetheless, the finding that considerable recurrence being diagnosed after 2 years suggests the need for follow up even after 2 years and angiography may be considered even though MRA findings suggest stable outcome.

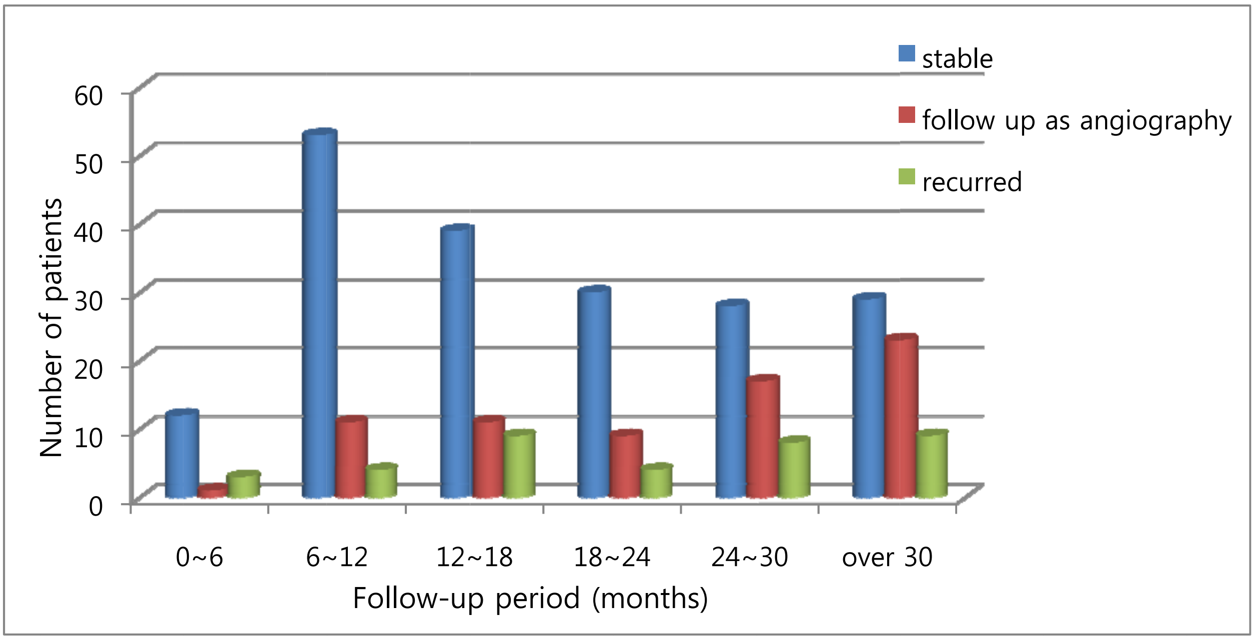

Figure 3. Number of stable and recurred aneurysm according to follow up periods.

The classification of treatment outcome and recurrence are subjective evaluations that might differ from one center to another.[28] Few pixels of stagnant dye may be insignificant for some interventionists but it may be considered incomplete occlusion or reopening for others. In this study, the initial treatment outcome was classified only into 3 categories since further subdivision can result in increased observer to observer bias.

The final objective of this study is to define patient category with minimal and maximal risk of recurrence. Small (<5 mm) and unruptured aneurysms, regardless of stent usage or complete outcome, had only 2.2% (2 of 89 aneurysms) of recurrence rate on mean 19.7 months follow up with 19.1% (17 of 89 aneurysms) confirmed by angiography. Small ruptured aneurysms had slightly higher recurrence rate of 22.2% (4 of 18 aneurysms). Larger (>10mm) aneurysms regardless of other characteristics had 40.9% (9 of 22 aneurysms) of recurrence rate. This study, however, does not justify the routine coil embolization for small unruptured aneurysms since the safety factors were not included and surgical option provides comparable result as well.

Although reported risk of rebleeding from recurred or remnant aneurysms are low,[18-20] patients now have longer life expectancy and mandate clinicians to be aware of the possibility for recurrence or rebleeding. Optimal treatment plan must be sought at first treatment since second treatment may not always be feasible. The search for factors affecting the durability of coiled aneurysm may be further clarified with prospective systematic follow up angiography protocols for further analysis of long term results.

V. CONCLUSION

Overall recurrence rate of coiled aneurysm was 16.2% (37 of 228 aneurysms) after an average of 19.5 months follow up. The possible risk factors that affect the durability of coil embolization were larger aneurysm volume, treatment after rupture, and absence of stent remodeling. These factors may be considered for clinicians in case of deciding for coil embolization of intracranial aneurysms and long term follow up may be needed in presence of such risk factors.

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ABSTRACT (IN KOREAN)

두개강내 동맥류의 코일 색전술후 내구력과 관련된 인자

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권 영 섭

목적: 혈관내 코일 색전술은 수술적 치료와 더불어 파열성 또는 비파열성 두개강내 동맥류의 치료에 중요한 치료 방법이다. 본 연구는 환자의 특성, 동맥류의 특성과 치료 및 추적검사의 결과를 분석하여 코일 색전술의 내구력과 관련된 인자를 분석하고자 한다.

재료 및 방법: 2005년부터 2009년 사이에 본원에서 동맥류 코일 색전술로 치료받은 환자에 대한 데이터를 후향적으로 검토하였다. 환자의 특성, 동맥류의 특성과 치료 및 추적검사의 결과를 수집하여 내구력과 관련된 인자를 통계학적으로 분석하였다.

결과: 총 208명의 환자에서 228개의 동맥류에 대한 특성, 치료 및 추적검사에 대한 자료를 분석하였다. 치료 후 평균 19.5개월의 추적검사 기간 동안 37 (16.2%) 개의 동맥류에서 재발을 보였다. 환자의 특성 중에선 파열된 상태로 치료를 했을 경우 재발과 유의한 결과를 보였다. 동맥류 인자 중 크기, 파열 여부, 동맥류의 깊이, 부피, 병목비와 측면비 등이 재발과 연관이 있었다. 치료 인자 중에서는 이용된 코일의 길이, 패킹 밀도, 스텐트 삽입 여부 와 치료의 완전성 등이 재발과 연관을 보였다. 추적검사의 기간과 추적검사의 방법으로서 뇌혈관 조영술 또한 재발과 유의한 관련을 보였다. 다변량 로지스틱 해석에서는 동맥류의 부피와, 파열후 치료

및 스텐트의 사용 여부의 인자가 코일 색전술후 재발의 유의한 인자로 예측되었다.
결론: 이 연구에서 동맥류의 부피, 파열후 치료와 스텐트 사용 여부등이 코일 색전술후 재발과 연관된 인자로 분석되었다. 이러한 인자들은 두개강내 동맥류의 코일 색전술시 고려되어야 하겠으며 위 인자를 가지고 있는 경우 장기간의 추적검사를 필요로 할 것이다.

핵심되는 말: 코일 색전술, 두개강내 동맥류, 내구력, 인자