Risk Factors for Intraprocedural Rupture in the Endovascular Treatment of Unruptured Intracranial Aneurysms: A Single-Center Experience with 1232 Procedures

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■ BACKGROUND: **Intraprocedural rupture (IPR) is a rare complication that can occur during endovascular treatment (EVT) of unruptured intracranial aneurysms (UIAs). However, it universally leads to poor outcomes if not properly managed. In the present study, we sought to illuminate the risk factors for IPR during EVT of UIAs.**

■ METHODS: **The data from patients with UIAs who had undergone EVT in our center from January 2010 to March 2017 were retrospectively collected and reviewed. Univariate analysis and multivariate logistic analysis were performed to analyze the risk factors for IPR.**

■ RESULTS: **A total of 1232 patients with 1312 unruptured aneurysms were included in the present study. IPR occurred in 11 patients (0.9%). Univariate analysis showed that cardiac comorbidities, irregular morphology, and location at the anterior communicating artery (AcomA) were significantly associated with the development of IPR ($P < 0.05$). In addition, stent placement was related to a lower risk of IPR compared with no stent placement ($P = 0.024$). The multivariate analysis showed that cardiac comorbidities (odds ratio [OR], 6.320; $P = 0.016$), irregular morphology (OR, 9.562; $P = 0.001$), and location on the AcomA (OR, 6.971; $P = 0.006$) were independent risk factors for IPR.**

■ CONCLUSIONS: **The occurrence rate of IPR was relatively low. Cardiac comorbidities, irregular morphology, and location on the AcomA are independent risk factors for IPR. Stents and flow diverters are safe and feasible in treating UIA, with a significantly low risk of IPR.**

INTRODUCTION

Endovascular treatment (EVT) has been increasingly used in the management of intracranial aneurysms, especially in unruptured intracranial aneurysms (UIAs).[1,2] Although the clinical outcomes of most EVT cases will be comparable and satisfactory, the risk of procedure-related complications leading to permanent deficit or mortality should not be ignored. Intraprocedural rupture (IPR) is 1 of the potentially fatal complications.[3-5] Nevertheless, the risk factors for IPR remain unclear and have not been fully investigated in previous studies. In a previous large-population cohort study, the occurrence rate of IPR in UIAs was 0.7%.[6]

The risk factors for IPR have been reported in several clinical studies.[4,7-9] However, few studies have provided sufficient evidence owing to the low incidence of IPR. In addition, most previous studies investigated the risk factors for IPR by merging both ruptured aneurysms and UIAs. Because of the differences in the natural course between ruptured aneurysms and UIAs, these should be investigated separately. For the first time, Kawabata et al.[6] reported the risk factors for IPR in UIAs using data from 1375 patients. They reported that aneurysms in the anterior communicating artery (AcomA) and those with a small dome size were likely to be risk factors for IPR.[6] However, limitations of their study should also be noted, including that data

Key words
- Endovascular treatment
- Intraprocedural rupture
- Unruptured intracranial aneurysms

Abbreviations and Acronyms
AcomA: Anterior communicating artery
EVT: Endovascular treatment
IPR: Intraprocedural rupture
mRS: Modified Rankin scale
OR: Odds ratio
SAH: Subarachnoid hemorrhage
UIA: Unruptured intracranial aneurysm

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regarding middle cerebral aneurysms, cardiac comorbidities, and aneurysmal morphology were not analyzed, which could have affected the results. In the present study, we performed a more comprehensive analysis of the risk factors related to IPR and present the clinical outcomes of those patients from a large population sample.

METHODS

Study Design and Data Source

A retrospective database was established that was approved by the Changhai Hospital affiliated ethics committee. All patients provided written informed consent. Patients with UIAs managed with EVT from January 2010 to February 2017 were enrolled. Data, including patient, aneurysmal, and procedure-related characteristics, were collected. Detailed risk factors included age, sex, preoperative modified Rankin scale (mRS) score, previous hypertension, diabetes mellitus, smoking status, alcohol use, history of cardiovascular disease and/or cardiac comorbidities, history of cerebral hemorrhage, history of cerebral ischemia, aneurysmal size, location, neck size, morphology, modality of treatment, flow diverting device, and number of stents. Preoperative neurological status (mRS) and follow-up outcome data were also included.

The inclusion criteria were as follows: consecutive patients with UIAs; receipt of EVT; and saccular UIAs. The exclusion criteria were fusiform, dissecting, traumatic, blister, and mycotic UIAs; UIAs associated with dural arteriovenous fistulas, arteriovenous malformation, moyamoya disease, or tumor; aneurysm-like dilatation; previous subarachnoid hemorrhage (SAH) or intracranial hemorrhage within 1 month; and incomplete data available.

Variable Definition

IPR was defined as angiographic contrast extravasation beyond the confines of the aneurysm wall. If an IPR occurred, heparin was immediately reversed with protamine, and the coiling was completed as rapidly as possible. The aneurysmal size was defined as the maximum size of each aneurysm. Cardiac comorbidity was defined as a history or presence of any heart disease (e.g., coronary artery disease, cardiac infarction, myocardiosis). Multiplicity indicates multiple intracranial aneurysms in a single patient. Irregular morphology was defined as aneurysms with daughter sacs or a lobulated shape.

The following data were included:

1. Patient-related factors: age (years), sex (female vs. male), previous hypertension (yes vs. no), diabetes mellitus (yes vs. no), history of SAH (yes vs. no), preoperative mRS score (0–1 vs. $\geq$2), previous ischemic attack or cerebral infarction (yes vs. no), cigarette consumption (current or previous smoker with smoking index >300 year branch (smoking year multiply branch per day); yes vs. no), alcohol consumption (current or previous abuse; yes/no), cerebral vascular stenosis (yes/no).
2. Aneurysm-related factors: aneurysmal size (mm), wide neck (neck size >4 mm or dome/neck ratio <1.5; yes vs. no), multiplicity (yes vs. no), location (internal carotid artery vs. other), location (anterior circulation vs. posterior circulation), and irregular morphology (yes vs. no).
3. Treatment-related factors: treatment modality (coiling only vs. stent only vs. stent-assisted coiling vs. balloon-assisted coiling vs. parent artery occlusion), variety of coils (not used vs. bare coils vs. modified coils), stent property (not used vs. routine stents vs. flow diverter), number of stents (not used vs. single vs. multiple), and multiple aneurysms treated in a single procedure.

The probability of neurological complications was evaluated by procedure rather than by individual aneurysm or patient. In the

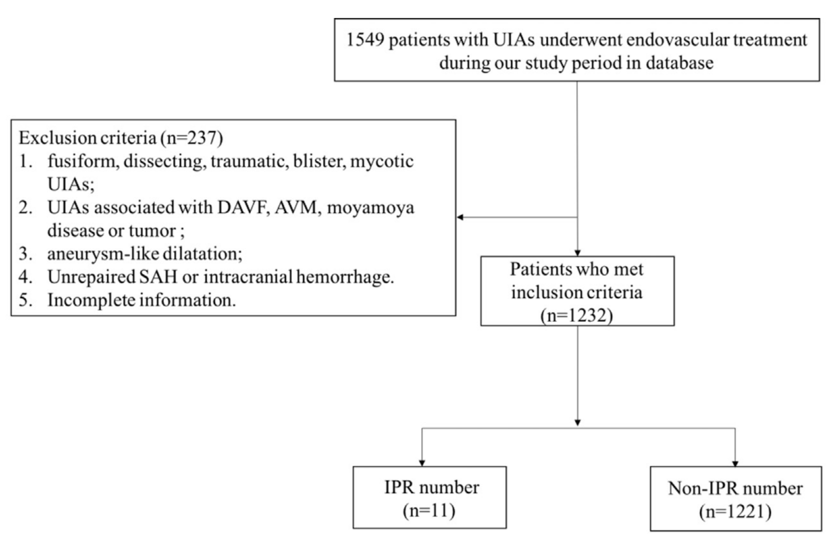

Figure 1. Study flowchart of patient recruitment. AVM, arteriovenous malformation; DAVF, dural arteriovenous fistula; IPR, intraprocedural rupture; SAH, subarachnoid hemorrhage; UIAs, unruptured intracranial aneurysms.

Table 1. Patient Characteristics and Univariate Analysis Results Stratified by Intraprocedural Rupture

Characteristic	Non-IPR (n = 1221)	IPR (n = 11)	P Value
Patient related			
Age (years)	57.42 ± 11.05	55.09 ± 14.15	0.200
Female gender	828 (68)	9 (82)	0.505*
Previous SAH	56 (5)	1 (9)	0.407†
Preoperative mRS score			1.000†
0–1	1189 (97)	11 (100)	
>2	32 (3)	0 (0)	
Previous hypertension	576 (47)	5 (46)	0.909
Diabetes mellitus	105 (9)	2 (18)	0.247
Cigarette consumption	92 (8)	0 (0)	1.000
Alcohol consumption	33 (3)	0 (0)	1.000
Previous TIA or CI	163 (13)	2 (18)	0.987*
Cardiac comorbidities	72 (6)	3 (27)	0.025†‡
Cerebral vascular stenosis			0.154
Absent	1118 (92)	9 (82)	
Proximal	27 (2)	0 (0)	
Distal	76 (6)	2 (18)	
Aneurysm related			
Size (mm)	7.40 ± 8.119	4.67 ± 1.871	0.097‡
Maximum size			0.076‡
≤3 mm	237 (19)	0 (0)	
>3 but ≤10 mm	748 (61)	10 (91)	
>10 but ≤25 mm	182 (15)	1 (9)	
>25 mm	54 (4)	0 (0)	
Neck size (mm)	4.64 ± 3.247	3.21 ± 1.342	0.142
Wide neck	1053 (86)	10 (91)	0.636
Location			0.009‡§
ACA, AcomA	135 (11)	4 (36)	
MCA	116 (10)	2 (18)	
ICA	915 (75)	3 (27)	
Other	55 (4.5)	2 (18)	
Anterior circulation location	1166 (96)	9 (82)	0.132†
AcomA location	110 (9)	4 (36)	0.014*‡
Perforator-rich vessel area	113 (9)	1 (9)	1.000*
Multiplicity	319 (26)	1 (9)	0.349*
Irregular morphology	149 (12)	6 (55)	0.001*‡
Maximum size			
≤5 mm	634 (52)	7 (63)	0.439
≤7 mm	841 (69)	10 (91)	0.188*
Treatment related			
Treatment modality			0.049‡§
Coiling only	145 (12)	5 (46)	
Stent-assisted coiling	1055 (86)	6 (55)	
Balloon-assisted coiling	14 (1)	0 (0)	
Parent artery occlusion	7 (1)	0 (0)	
Stent property			0.024‡§
Not used	166 (14)	5 (46)	
Routine stents	973 (80)	6 (55)	
Flow diverting device	82 (7)	0 (0)	
Stents			0.107§
Not used	166 (15)	5 (46)	
Single	924 (76)	5 (46)	
Multiple	131 (11)	1 (9)	
≥2 Aneurysms treated in 1 procedure	83 (7)	0 (0)	1.000†

IPR, intraprocedural rupture; SAH, subarachnoid hemorrhage; mRS, modified Rankin scale; TIA, transient ischemic attack; CI, cerebral infarction; ACA, anterior cerebral artery; AcomA, anterior communicating artery; MCA, middle cerebral artery; ICA, internal carotid artery.
*Continuity correction of χ^2.
†Fisher exact test.
‡Statistically significant and included multivariate analysis.
§Likelihood ratio.

case of multiple aneurysms treated in a single procedure, the features of the aneurysm considered potentially responsible for the neurological complications were included in the analysis.

Statistical Analysis

Statistical analysis was performed using SPSS, version 23.0 (IBM Corp., Armonk, New York, USA). Continuous variables are reported as the mean ± standard deviation and categorical variables as numbers and percentages. The categorical variables were compared using the Pearson χ^2 test or Fisher exact test. Univariate analysis was performed to identify the potential variables associated with IPR. Clinical variables with $P < 0.10$ on univariate analysis were included in the multivariate logistic regression model. A 2-tailed $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics

A total of 1549 UIAs were treated from January 2010 to March 2017 in our center. Of these, 1050 patients with 1312 UIAs who had undergone 1232 procedures met the inclusion and exclusion criteria and were enrolled in the present study (Figure 1). The included patients were categorized into non-IPR and IPR groups according to whether IPR had occurred. Of the 1050 patients, IPR occurred in 11, for a rate of 0.9% (11 of 1232 procedures).

The patient characteristics are presented in Table 1. The average age of the non-IPR group and IPR group was 57.42 ± 11.05 and 55.09 ± 14.15 years, respectively. The non-IPR and IPR groups included 828 (68%) and 9 (81%) female patients, respectively. Of the 1050 patients, 412 (30%) had multiple aneurysms. Hemorrhagic complications occurred in 19 patients (1.5% of 1232 procedures), with IPR in 11 patients, for an incidence rate of (0.9% of 1232 procedures). Postoperative computed tomography scanning found 8 cases of cerebral hemorrhage, for an incidence rate of 0.6% of 1232 procedures.

Risk Factors for IPR

The univariate analysis results are listed in Table 1. Cardiac comorbidities, aneurysm size, irregular morphology, variety of coils used, and location on AcomA were significantly associated with the occurrence of neurological complications ($P < 0.1$) and were included in the multivariable analysis. The mutivariable logistic regression model with backward stepwise variable analysis showed that cardiac comorbidities (odds ratio [OR], 6.957; $P = 0.007$), irregular morphology (OR, 8.769; $P = 0.001$), and AcomA location (OR, 5.954; $P = 0.006$) were independent risk factors for IPR (Table 2).

Clinical Features of Patients with IPR

The clinical features of the IPR patients are listed in Table 3. The cause of IPR was as follows: 2 occurred during the process of super-selection, 6 during coil placement, and 3 during angiography. The proportions of perforation by coils, microcatheter, and microwires were 54.5%, 18.2%, and 9.1%, respectively. However, the cause was uncertain in 2 patients, in whom IPR occurred during the process of angiography or super-selection. Of the 11 patients with IPR patients, 6 had completely recovered immediately or immediately after salvage management (mRS score, 0). However, 1 patient experienced permanent disability. Even after immediate salvage management, 4 patients died of extensive SAH, with a Hunt and Hess grade of 4—5. Regarding salvage management, 4 patients (36%) experienced acute onset of hydrocephalus and underwent external ventricular drain placement, 4 (36%) underwent balloon hemostasis, and 2 (18%) underwent lumbar puncture. For the 11 patients with IPR, the morbidity and mortality rate was 9% and 36%, respectively.

DISCUSSION

EVT has been widely accepted and proved to be safe and feasible with comparable occlusion rates and clinical outcomes in the management of UIAs in several studies.[10,11] However, IPR, which is devastating and can result in deteriorated clinical outcomes, should be highlighted. The early diagnosis and management of IPR can lead to a comparable clinical outcome for most patients.[12] In our study, the incidence of IPR was relatively low (0.89%) compared with the incidence reported in previous studies.[9,13,14] Also, the morbidity rate for the patients with IPR was 9.1% (1 of 11), and the mortality rate was 36.4% (4 of 11) in our study.

Table 2. Multivariate Analysis of Hemorrhagic Complications

Variable	OR	95% CI	*P* Value
Cardiac comorbidities	6.957	1.713—28.265	0.007
Irregular morphology or daughter sac	8.769	2.577—29.837	0.001
AcomA location	5.954	1.648—21.514	0.006

OR, odds ratio; CI, confidence interval; AcomA, anterior communicating artery.

IPR has been reported in several previous studies in both ruptured aneurysms and UIAs. Zang et al.[15] collected data from 437 consecutive patients with 507 cerebral aneurysms (137 patients with unruptured aneurysms and 370 with ruptured aneurysms). They found that IPR was more likely to occur in small aneurysms and was associated with relatively high rates of mortality ($n = 3$; 21.4%).[15] A meta-analysis of EVT for very small intracranial aneurysms, performed by Yamaki et al.,[16] included 21 studies with 1105 tiny aneurysms (844 ruptured and 261 unruptured). The rate of IPR in tiny aneurysms was 7%.[16] Fang et al.[17] performed a meta-analysis of 14 studies with 1552 AcomA aneurysms managed with EVT. IPR occurred in 4% of those patients.[17]

Table 3. Clinical Characteristics of Patients with Intraprocedural Rupture

Characteristic	Patients (*n*, %)
Timing of perforation	
Super-selection	2 (18)
Coil placement	
Framing	1 (9)
Filling	4 (36)
Finishing	1 (9)
Angiography	3 (27)
Cause of perforation	
Coils	6 (55)
Microcatheter	2 (18)
Microwires	1 (9)
Uncertain	2 (18)
Hunt and Hess grade 4—5	4 (36)
Salvage management	
EVD placement or salvage surgery	4 (36)
Hydrocephalus	4 (36)
Cerebral infarction	1 (9)
Clinical outcome	
Morbidity	1 (9)
Mortality	4 (36)

EVD, extraventricular drain.

However, few studies have investigated the risk factors associated with IPR or provided robust evidence with sufficient case numbers, included only patients with UIAs, or included specific risk factors.[9,18] Kawabata et al.[6] retrospectively reviewed the data from 1375 patients with 1406 UIAs treated with coil embolization. The results showed that AcomA location and a small dome size are likely to be risk factors for IPR.[6] In the present study, we have provided a large sample-based analysis and investigated possible risk factors, including aneurysmal morphology, cardiac comorbidity, variety of coils used, stent properties, and number of stents. These had rarely been investigated in previous studies. Multivariate analysis revealed that cardiac comorbidities (OR, 6.320; $P = 0.016$), irregular morphology (OR, 9.562; $P = 0.001$), and AcomA location (OR, 6. 971; $P = 0.006$) were independent risk factors for IPR.

Cardiac comorbidity was an important predictor of IPR in our study, which has not been previously reported. UIAs in patients with previous heart disease were much more likely to rupture. Irregular morphology and the presence of a daughter aneurysm or bleb have been widely considered predictors of rupture during aneurysm formation and growth[19-21] and was related to rupture status.[22] In our study, irregular morphology (OR, 9.562; $P = 0.001$) was an independent robust predictor of IPR, which has also been reported in previous studies.[1] In addition, an AcomA location was a predictor of IPR, consistent with the results reported by Kawabata et al.[13] Owing to the tortuous and cramped anatomic characteristics of the AcomA, such as unfavorable dome/neck ratio and acute internal carotid artery—anterior cerebral artery angle, endovascular embolization might be difficult to be completed accurately.[23] The The Unruptured Cerebral Aneurysm Study Japan investigators reported that UIAs located on the AcomA, including small UIAs, had a high risk of rupture.[19]

Several other factors were also reported to be related to the occurrence of IPR. A previous prospective multicenter study of 700 patients with UIAs reported that aneurysmal size was also significantly associated with the occurrence of IPR.[24] However, Mitchell et al.[25] reported a study of 689 aneurysms, with 595 patients treated with coiling. They found that aneurysm size <4 mm was a risk factor for IPR in ruptured, but not unruptured, aneurysms.[25] In our study, the correlation between aneurysmal size and the risk of rupture was also not statistically significant ($P = 0.439$).

According to our analysis, we hypothesized that the risk factors associated with aneurysmal rupture in the natural course could also be risk factors for IPR, considered a superimposing effect. Several other influential factors could be analyzed in further studies, including wall shear stress, material properties, and others. In a biomechanical analysis, intracranial aneurysmal pulsatility was considered a predictor in a rupture risk evaluation.[26] Material properties have also been reported to influence the systolic/diastolic aneurysmal volume variations and was also used as a biomechanical index of rupture risk.[27]

The relationship between stent placement and IPR was also investigated in our study. We found that stent placement was a protective factor against IPR on univariate analysis. The incidence rate of IPR in patients treated with stents or flow diverters was significantly lower than that of patients treated without stents (2.9%, [5 of 171] vs. 0.6% [6 of 1061]; $P = 0.009$). In addition, most patients in our institution were treated with stents or flow diverters (86.1% [1061 of 1232 procedures]), which might have contributed to the low incidence rate of IPR. Thus, the application of stents or flow diverters in the treatment of UIAs can be considered safe and feasible. To minimize injury and maximize the outcomes from IPR, a potential protocol could include the following. First, for patients with UIAs and a high risk of IPR, salvage treatment, including balloon and hemostatic medications should be prepared before surgery. Second, stent placement could improve the occlusion rate of the aneurysmal sac and decrease the number of coils.

The present study had some limitations. First, we performed a retrospective clinical study using a single-center database. Considering the low incidence rate of IPR, a detailed analysis of the data from the patients with IPR was not possible. In addition, although the differences for some risk factors such as the variety of coils and stents were not statistically significant, our conclusions should also be validated in further multicenter investigations. Second, the clinical outcomes of patients with IPR were relatively poor. The mortality (4 of 11) of the patients with IPR was relatively greater compared with that reported from previous studies. One possible explanation might be that the Hunt and Hess grade at immediate hemorrhage was quite high (Hunt and Hess grade, 4—5) in our study. Four patients died although salvage management had been immediately performed. In addition, IPR occurred during the process of super-selection or the delivery of guiding catheter in 2 patients.

CONCLUSIONS

The occurrence rate of IPR has been relatively low and should be managed with immediate salvage. Cardiac comorbidities, irregular morphology, and AcomA location were independent risk factors for IPR. Stent placement was safe and feasible in treating UIAs and will not lead to IPR.

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