Iranian Journal of NEUROSURGERY

April 2018, Vol 4, Issue 2, No 13

Research Paper:
Outcome of In-Hospital Rebleeding and Early Aneurysm Rupture at the Referral Centers

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Citation: Rahmanian A, Derakhshan N, Ali Alibai E. Outcome of In-Hospital Rebleeding and Early Aneurysm Rupture at the Referral Centers. Iran J Neurosurg. 2018; 4(2):93-100. http://dx.doi.org/10.32598/irjns.4.2.93

doi: http://dx.doi.org/10.32598/irjns.4.2.93

Funding: See Page 99

Article info:
Received: 17 October 2017
Accepted: 20 January 2018
Available Online: 01 April 2018

Keywords:
Cerebral aneurysm, Ruptured aneurysm, Tertiary referral hospital, Outcome, Incidence

ABSTRACT

Background and Aim: In-hospital rebleeding and early aneurysm rupture are major causes of mortality and morbidity in aneurysmal subarachnoid hemorrhage. Rebleeding may occur at the referring hospital, during transfer or at the referral neurovascular center prior to surgical or endovascular treatment. However, there has been no report regarding the rate of in-hospital rebleeding and early aneurysm rupture at the referral centers. This study aims to clarify the incidence, significance, management, and outcome of individuals who suffer in-hospital aneurysmal rebleeding and early aneurysm rupture at the referral hospital due to anterior circulation cerebral aneurysm to the time when its neck is visualized for clipping.

Methods and Materials/Patients: Among 617 patients with anterior circulation cerebral aneurysms, who underwent operation between September 2010 and September 2017 at Neurovascular Unit of Namazi Hospital (main referral neurovascular center in southern Iran), 22 suffered rebleeding since the time of neuroradiologic diagnosis of aneurysm to intraoperative visualization of aneurysm for neck dissection. A surgical technique for fast access and securing the aneurysm is described in this article, too. The patients' demographics were collected via hospital records in a retrospective fashion. Six-month functional outcome was obtained via OPD records as well as phone calls. Performing Independent t test, 1-way ANOVA, Kruskal-Wallis and Mann-Whitney tests in SPSS22, the effect of each study variable was evaluated during 6 months follow-up period.

Results: Rebleeding occurred at different venues from CT angiography to frontal lobe retraction. Anterior communicating artery was the most common aneurysm to suffer in-hospital rebleeding and male gender was found as a risk factor. These patients have significantly higher bleeding amount and longer operative time (P<0.001), but still have a 68.2% chance of survival with good functional recovery. Earlier in-hospital rebleedings used to have worse outcomes (P=0.036 for GOS and 0.028 for mRS, respectively).

Conclusion: Patients with in-hospital rebleeding and early aneurysm rupture at the referral hospitals will have a considerable chance for favorable outcome if they undergo aggressive surgical management emergently.

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Highlights

- Almost 3.5% of patients with cerebral aneurysms suffer early re-bleeding at the referral hospital.
- Contrary to previous reports, we believe that these patients have a good prognosis.
- The surgical technique presented here, provides an early access for proximal control and clipping the aneurysm.
- Sixty-eight percent of patients, who suffered early rupture, had a favorable outcome.

Plain Language Summary

Brain aneurysm is defined as a localized ballooning in a certain area of the arterial vessels in brain. At this spot, the vessel wall is weak and prone to rupture. When ruptured, cerebral aneurysm presents with a certain type of stroke called subarachnoid hemorrhage. Subarachnoid hemorrhage due to the ruptured cerebral aneurysm should be stabilized primarily by securing patient's airway and maintaining normal oxygenation, controlling high blood pressure and seizures. After primary stabilization, the patients should be transferred to a tertiary referral hospital, equipped by neuroimaging diagnostic tools, vascular neuro-intervention unit and a neuro-vascular microsurgery unit. During diagnostic evaluations at the tertiary referral hospital and prior the securing the aneurysm, a considerable number of patients experience re-bleeding. Re-bleeding, as recurrence of hemorrhage from the aneurysm, has been shown to be accompanied with a dismal prognosis. However, during their admission at the referral hospital, many of such patients can still have a favorable outcome if managed in a timely fashion. Microvascular surgery in these patients is quite challenging due to severe brain swelling and the surgical field being filled with blood which obscures surgeon's vision and further complicates the surgery. Here, we present a surgical technique for early access to secure the aneurysm. With the provided technique, we have achieved favorable outcomes in as much as 68% (15 of 22) of patients.

1. Introduction

Cerebral aneurysms are the commonest cause of spontaneous Subarachnoid Hemorrhage (SAH) worldwide. Despite recent advances in aggressive endovascular therapy, surgical techniques, and neurocritical care, aneurysmal Subarachnoid Hemorrhage (aSAH) is still associated with high rate of mortality and morbidity. Many deaths after aSAH are due to the initial hemorrhage and occur very rapidly [1]. However, in hospitalized patients, even in neurovascular centers with pioneering early definitive treatment [2], rebleeding is still the most important preventable cause of poor outcome, followed by vasospasm, and hydrocephalus [3].

Rebleeding occurs at a rate of about 3.4% to 17.3 % according to different studies[3, 4]. Rebleeding rates have significantly declined since the establishment of "modern management" [2] principles which emphasize on the early surgical or endovascular intervention. However, despite the inclusion of early management in the acute phase of aSAH within less than three days of the initial hemorrhage, rebleeding still occurs and is associated with high mortality and morbidity [4, 5].

Risk factors for rebleeding are low Glasgow Coma Scale (GCS) score [3, 4, 6], poor Hunt and Hess (H&H) clinical grades 3 or 4, high systolic blood pressure [4, 7], systolic blood pressure variability [8], intraventricular or intracerebral hematoma [4, 9], number of aneurysms [10], and undergoing angiographic evaluation within 6 hours of SAH [4]. Genotyping assays performed on blood samples of patients with aSAH have detected common endothelin Single Nucleotide Polymorphism (SNP) on blood samples of patients with aSAH and identified TT genotype of EDN1 G/T SNP as an independent risk factor [11].

Many authors agree that rebleedings are more prevalent within the first 24 hours, whereas others believe that they occur at a later period after initial hemorrhage [6, 12]. The data regarding the effect of aneurysm size on rebleeding risk are variable and inconsistent [13-15]; however, most neurovascular authorities agree that certain features (e.g. blood-blister like carotid aneurysms) [16, 17] and projections [18] leave the aneurysm at a higher risk for re-rupturing.

Previous studies indicate that mortality of aggressive treatment of patients, who experience rebleeding, is as high as 50% to 80 % and the survivors had a poor

functional outcome [8, 19, 20]. Data regarding the efficacy of antifibrinolytics in prevention of rebleeding are equivocal [21] and early surgery still remains the only hope they have for survival. Here, following the establishment of "modern management" in our neurovascular unit, we reviewed the demographic features, risk factors, operative data and functional outcome of all 22 salvageable patients with aSAH, who experienced rebleeding or intraoperative rupture at the referral hospital prior to successful clipping of their aneurysms.

This study aims at describing the surgical technique and functional outcome of patients (and its determinants), who experienced early in-hospital rebleeding at this tertiary neurovascular center.

2. Methods and Materials/Patients

Study population

In this retrospective study, a total of 648 patients with anterior circulation aneurysms, who were operated between September 2010 and September 2017 at Neurovascular Unit of Namazi Hospital (main referral neurovascular center in southern Iran) [22, 23], were investigated. After exclusion of those who were lost to follow up and the ones whose hospital records were incomplete and inaccessible, 617 were remained eligible as the reference population. Of them, 22 patients suffered from in-hospital rebleeding and early rupture between the diagnostic neuroimaging modality (CT angiography) and visualization of aneurysm neck for dissection. They were included in this survey.

Surgical technique

Regardless of routine neuro-anesthetic protocols for every patient with SAH due to cerebral aneurysm, rebleeding was diagnosed differently in each situation and surgery was performed. The current policy in our neurovascular center is diagnostic confirmation of aneurysm by CT Angiography (CTA) and saving 4-vessel catheter angiography for those who require confirmatory evaluations as well as collateral circulation survey. All salvageable 22 cases of in-hospital rebleedings had been diagnosed by CTA. Four patients who suffered from early rupture and in-hospital rebleeding prior to surgery were operated urgently after their sudden loss of consciousness and confirmation of rebleeding by brain CT scan.

Before anesthesia, rebleeding was noticed via sudden changes in GCS as well as patients' pupils and a feel of severe sudden-onset headache in conscious patients. During and after induction of anesthesia, a sudden increase in blood pressure accompanied by decrease in heart rate (i.e. the Cushing phenomenon) in a previously stable patient was identified as rebleeding. After opening the dura matter through frontal lobe retraction, a sudden aggressive brain swelling was the case. We used a Frazier suction tube 12 French, and bipolar cautery to perform a wedge shaped frontal lobectomy to access the internal carotid artery through the fastest route (Figure 1B). Then temporary clip is applied on main feeder artery and using a cotton-ball and suction, a pilot clip is applied on the bleeder point which is further re-adjusted to occlude the aneurysm sac (or reconstruct the arterial lumen in cases of blister-like carotid aneurysms via double-clip technique).

Clipping time was considered the time between opening the dura matter and confirmation of successful clipping by video-angiography. Successful occlusion of aneurysm and patency of parent artery and branches are confirmed via Indocyanine Green (ICG) video-angiography as well as intraoperative Doppler ultrasonography. We carried out lateral supra-orbital craniotomy for all these patients.

Data collection

An information form was filled out for each patient by reviewing hospital records, critical care documents, as well as surgery notes, and finally the contact details. Functional outcome after 6 months was obtained through phone calls as well as out-patient records that stated in terms of the Glasgow Outcome Scale (GOS) and the modified Rankin Scale (mRS).

Statistical analysis

All the statistical analyses were performed in SPSS (SPSS Inc., Chicago, Illinois, USA) version 22.0. The obtained data are reported as mean±SD. The Independent t test, 1-way ANOVA, Kruskal-Wallis and Mann-Whitney tests were utilized to examine the effect of each variable on the outcome of patients after 6 months, as appropriate.

3. Results

Between September 2010 and September 2017, 617 patients underwent operation due to anterior circulation aneurysms. Of them, 22(3.56%) suffered from aneurysm in-hospital rebleeding and early intra-operative rupture at the referral hospital. The patients had a Mean±SD age of 47.27±11.53 years. They comprised 13 men and 9 women (M: F ratio 1.44) compared to the ref-

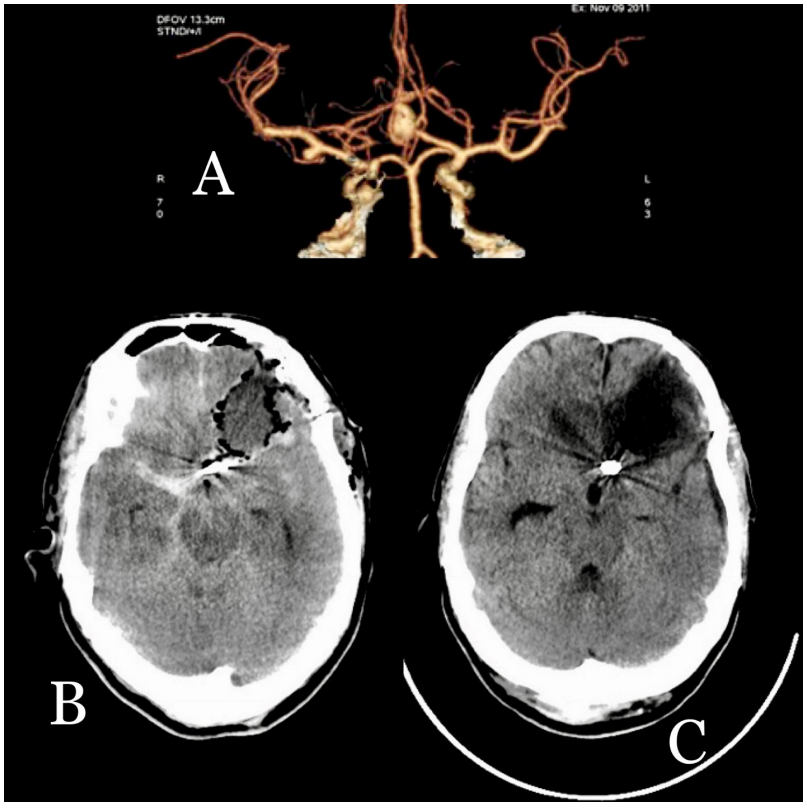

Figure 1. Early rupture of an ACOM aneurysm

A: Brain CT angiogram of a 48-year-old man who had a cerebral aneurysm at anterior communicating artery (GCS: 15) and suffered from early rebleeding. B: After the occurrence of rebleeding during CT angiography, which was diagnosed with acute loss of consciousness (GCS: 6 and bilateral midsized fixed pupils), the patient was immediately transferred to operating room and via a lateral supraorbital craniotomy, the dura was opened. Because of severe brain swelling, a wedge of frontal lobe was resected to gain access to aneurysm neck, and the clip was successfully applied. C: Brain CT after 6 months when the patient had no neurological deficits and with an mRS of 0.

erence population with the Mean±SD age of 48.12±4.42 and M: F ratio of 0.95. Neither age nor gender were associated with functional outcome at 6-month follow-up. GCS and H&H clinical grade at admission were correlated with the outcome. Most patients had modified Fischer grade 3 or 4 on CT scans (86.36%), but no correlation was found between Fisher grade and presence of IVH and ICH with functional outcome.

In-hospital rebleeding and early intraoperative rupture occurred at different situations and time frames between initiation of brain CT angiography and intra-

Table 1. Correlation of Demographics and Initial Clinical Scores with Outcome

Demographic Features	Mean±SD	Association With Functional Outcome After 6 Months	
		GOS	MRS
Age, y	47.27±11.53	0.32	0.33
Gender		0.31	0.407
GCS	11.31±4.37	0.005	0.003
H&H	2.77±1.68	0.012	0.007
Fisher Grade		0.39	0.33

Table 2. Functional outcome of patients who suffered from rebleeding at the referral hospital 6 months after the operation

GOS	MRS	Frequency (%)
1	6	7(31.2)
4	2	4(18.2)
5	0, 1	11(50)

operative visualization of aneurysm neck. Two patients suffered rebleeding during CTA, two in the ICU before the planned operation (on the next operative day as the standard of our center), three during induction of neuro-anesthesia, two during incision and craniotomy, three during opening of dura matter and before frontal lobe retraction, and 10 during frontal lobe retraction.

According to mRS and GOS after 6 months, 15(68.2%) patients had favorable outcomes (MRS of 0, 1, and 2 plus GOS of 4 and 5) and 7(31.2%) died (Table 2).

Table 3. Correlation of Different Variables on Clinical Outcome at 6-months

Variable Factors		Frequency (%)	Significance for Outcome (P) of GOS and MRS at 6-Months	
Risk factors	Diabetes mellitus	2(9.1)	0.10	0.10
	Hypertension	10(45.4)	1	0.87
	Ischemic heart disease	1(4.5)		
	Cigarette smoking	10(45.4)	0.58	0.31
	Opium addiction	8(36.4)	0.87	0.92
Location	Anterior communicating artery	11(50)	0.24	0.16
	MCA Bifurcation	4(18.2)		
	PCOM	3(13.6)		
	Paraclinoid carotid (Blister-like)	2(9.1)		
	Ophthalmic	2(9.1)		
	Hydrocephalus	12(54.5)	0.52	0.38
Comorbidities	VP-Shunt insertion	3(13.6)	0.78	0.92
	Perioperative seizures	1(4.5)	0.36	0.36
Operative time			0.007	0.094
Bleeding amount			0.011	0.018
SAH-rebleeding/ operation	<24 h	13(59.2)	0.036	0.028
	1–7 days	4(18.1)		
	8–14 days	4(18.1)		
	>14 days	1(4.6)		

Patient's risk factors such as Hypertension (HTN), Diabetes Mellitus (DM), Ischemic Heart Disease (IHD), smoking and opium addiction were not correlated with the worse outcome. All patients had one aneurysm and distribution of the location of aneurysm in anterior circulation was demonstrated in Table 3, which did not show any correlation with the outcome. However, the frequency of Anterior Communicating Artery (ACOM) and carotid blister-like location was higher in this subset of patients compared to our reference population.

Perioperative seizures, hydrocephalus and need for ventriculoperitoneal shunt was not accompanied with worse outcome in this group of patients. However, operative time and bleeding amount were directly correlated with worse outcome (P values of 0.07 and 0.018, respectively). The Mean±SD values for clipping time and bleeding amount were 57.95±30.38 min and 893.18(955.22) mL, respectively which are significantly higher than the values for our standard procedure (P<0.001).

The interval between SAH and in-hospital rebleeding or early intra-operative rupture (followed by emergency aneurysm clipping) was less than 24 hours for 13 patients, 2–7 days for 4 patients, 8–14 days for 4 patients and more than 14 days for 1 patient. Earlier rebleeding was found to be associated with worse prognosis in terms of lower GOS (P=0.036) and higher mRS (P=0.028). Of 11 ACOM aneurysms with in-hospital rebleeding and early intraoperative rupture prior to aneurysm neck identification, 10 had superior and 1 had inferior projection.

4. Discussion

Although early surgical and endovascular management of cerebral aneurysms in the past two decades has declined the catastrophic results seen with in-hospital rebleeding and early intraoperative rupture beforehand, it is still the most important preventable comorbidity of aSAH along with vasospasm and hydrocephalus. Genetic studies have now confirmed that endothelin pleomorphism [11, 24-26] plays a crucial role in this scenario and we believe that the road to redemption goes through genomic and proteomic analysis of cerebral aneurysms. Considering demographic features in our series, we found a higher M:F ratio in those who sustained rebleeding; however, no correlation was found between gender and functional outcome. Our data were consistent with previous literature showing that better GCS and H&H grades were associated with better prognosis.

Zhao et al. also believed that patients, who sustain rebleeding will benefit from aggressive treatment [19]. They found that worse clinical grades (in terms of WFNS grade) and lower GCS after rebleeding resulted in poorer functional outcome. However, considering that we included many patients that are believed to sustain re-rupture during anesthesia or surgery, this comparison could not be made.

Notwithstanding high systolic blood pressure risk factor for aneurysm rebleeding [4, 7], we believe that premorbid hypertension does not worsen functional outcome. Diabetes mellitus, ischemic heart disease, smoking and opium addiction were not associated with a poor outcome either.

ACOM (with superior projection) and blood-blister like carotid aneurysm were found as the two locations at risk for rebleeding; however, neither of locations and projections was found to impose a greater risk for poor outcome in this series. Most patients of the presented series suffered from in-hospital rebleeding and early intraoperative rupture within the first 24 hours (59.2%). The interval between initial hemorrhage and rebleeding (followed by emergency clipping) was found to be inversely correlated with outcome which might be due to better feasibility of the aneurysm dissection and stabilization of the clot formed following initial hemorrhage.

Patients, whose operations were longer and suffered more bleeding amount, were also found to have poorer clinical outcomes. Two points should be considered as limitations to the current study. First is the sole inclusion of surgically-managed individuals in the investigation, as the equipment for endovascular management of such cases were not available due to sanctions imposed on Iran. Second is that we only operated anterior circulation aneurysms in the mentioned setting and posterior circulation aneurysms were not subject to this technique and tend to have a further worse prognosis in cases of rebleeding and none happened in the operation room.

Despite several reports on the dismal prognosis of in-hospital rebleeding [8, 19, 20], we found 68.2% favorable outcome (mRS=0, 1 and 2) in our series. We believe that the lobectomy with a large Frazier suction tip (Fr 12) in this technique provides the ideal surgical corridor for access to the aneurysm and its main feeders without causing significant neurologic damages (Figure 1; A, B and C). Even though, this series covers only patients with a single anterior circulation aneurysm, we believe that aggressive treatment should be the rule for similar

situations and provide the remarkable chance for a possible favorable outcome.

A limitation of this study is that all 22 patients underwent surgical management and no historical "control" group could be considered for comparison. That is probably due to further experience of our surgical team and the unavailability of endovascular equipment in an emergent setting at this neurovascular center.

5. Conclusion

Almost 3.5% of patients with cerebral aneurysm in anterior circulation suffered from in-hospital rebleeding and early intraoperative rupture at the referral hospital. Despite previous reports of the dismal prognosis of these patients, 15 out of 22 patients in our series survived with favorable outcomes (mRS of 0, 1, and 2 or GOS of 4 or 5). We believe that our surgical technique opens a window of hope for survival of such patients with a considerable chance of favorable outcomes.

Ethical Considerations

Compliance with ethical guidelines

There is no ethical principle to be considered doing this research.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contributions

The Authors contributions are as follows: Abdolkarim Rahmanian contributed to describing the surgical technic and conceptualization. Nima Derakhshan helped in writing the original draft and revised in its final format. Ehsan Ali Alibai revised the manuscript critically and contributed to conceptualization and methodology.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

Here we want to thank the patients participated in this investigation and also their families who helped with evaluation of outcome at follow-ups. We would also like to thank neurosurgery residents, neurosurgery operating room and Neuro-intensive care unit personnel who helped to make this center the largest tertiary neurovascular center of Southern Iran.

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