Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Clinical outcomes of multiple aneurysms microsurgical clipping: Evaluation of 90 patients☆

Murad Asiltürk [a,1], *Anas Abdallah* [b,1,*]

[a] *Department of Neurosurgery, Bakirkoy Research and Training Hospital for Neurology Neurosurgery and Psychiatry, 34147 Istanbul, Turkey*
[b] *Department of Neurosurgery, Bezmialem Vakif University, 34093 Istanbul, Turkey*

ARTICLE INFO

Article history:
Received 11 May 2017
Accepted 14 September 2017
Available online 23 September 2017

Keywords:
Multiple cerebral aneurysm clipping
Subarachnoid hemorrhage
Hunt–Hess scale
Counter laterally clipping aneurysm
Extensive drilling in aneurysm surgery

ABSTRACT

Background: The incidence of multiple intracranial aneurysms (MIAs) among patients who are diagnosed with aneurysm is 15–45% in the literature. Treatment options depend on the patient's status, age, aneurysm location and neurosurgeon's experience. In this study outcomes of micro-surgically clipped 90 patients have been evaluated.

Materials and methods: Medical records of 90 (49 women and 41 men) patients of MIAs who underwent surgery by the authors, during a 3-year period from 2011 to 2013 were retrospectively reviewed of prospectively collected patients' data. Surgically treated patients underwent a lateral supraorbital craniotomy followed by microsurgical clipping of all reachable aneurysms.

Results: The mean age of the sample is 50.8 ± 11.9 (25–82) years. There were 67 patients presented with SAH. The most common complaint was severe headache of sudden onset (94%) in SAH group and migraine type headache (60.8%) in incidentally diagnosed group. According to location of the arteries; ACoA (50), MCA (R:49,L:45), ICA (R:34,L:15), PCoA (R:9, L:4), ACA (R:6,L:4), basilar artery (3) and SCA (2). Mortality rate was 13.3% ($n = 12$), morbidity rate (new deficit was developed) was 18.8% ($n = 17$) [7 out of them were partially/completely dependent on others for daily living activities before surgery (i.e. GOS < 3)] and 67.8% ($n = 61$) of the patients returned to their normal jobs and daily activities.

Conclusions: Multiple cerebral aneurysms are not associated with a less favorable outcome than are single aneurysm cases. Authors prefer microsurgical clipping of all the aneurysms, be it on the reverse side, if the aneurysm location is reachable and that includes bilaterally presenting MIAs.

☆ This study was approved under decision number: (573) by the medical ethics committee of Bakırköy Research and Training Hospital for Neurology Neurosurgery, and Psychiatry (BRSHH) in Istanbul-Turkey.

* *Corresponding author at*: Department of Neurosurgery, Bezmialem Vakif University, Adnan Menderes Bulvari, Vatan Street, 34093 Fatih, Istanbul, Turkey.
E-mail addresses: muradasilturk@bakirkoyruhsinir.gov.tr (M. Asiltürk), aabdallah@bezmialem.edu.tr (A. Abdallah).

[1] Drs. Asiltürk and Abdallah contributed equally to this work.

http://dx.doi.org/10.1016/j.pjnns.2017.09.005

1. Introduction

Cerebral aneurysms occur in 1–2% of the population and account for about 80–85% of non-traumatic subarachnoid hemorrhages (SAH). Autopsy studies indicate prevalence in the adult population between 1% and 5%; however, 50–80% of all aneurysms do not rupture during the course of a person's lifetime. Unruptured intracranial aneurysms are more common in women as much as three times [1,2]. Some rare familial forms of aneurysms have been associated with conditions such as autosomal dominant polycystic kidney disease, Marfan's syndrome, Ehlers–Danlos syndrome type IV, fibromuscular dysplasia, Moyamoya disease, sickle cell disease, and arteriovenous malformations of the brain [1]. An important risk factor for aneurysm is the family history. Patients with one affected family member have approximately a 4% risk of having an aneurysm, whereas patients with 2 or more affected first-degree family members have an 8–10% risk of developing an aneurysm [1].

Despite the fact that no accurate number, we estimate that the incidence of SAH that related to ruptured cerebral aneurysms in Turkey is approximately 8/100,000 person-years (our hospital is one of main four reference centers in Istanbul, in which yearly operated on approximately 150 patients). SAH is more common in women than in men (2:1) with the peak incidence occurring in age group 50–60 years old [2,4]. The mortality rate for SAH is 8.3–66.7%, and as high as 3 in 5 of those who survive SAH may be functionally dependent [3].

It is still being debated when neurosurgeons have to treat unruptured aneurysms especially in multiple intracranial aneurysm (MIA) cases. It is well-known that aneurysms over years will grow and may get ruptured. The rupture risk assessments for MIAs are mainly based on morphology [1,3–8]. Hemodynamics play a fundamental role in aneurismal rupture [3,6–8]. It is largely unknown whether hemodynamic factors are also involved in modulating the risk of rupture in MIAs. Several studies showed that MIAs are associated with a less favorable outcome than are single aneurysm cases after SAH [2,8]. Herein, the authors reviewed their own microsurgical clipping experience for treatment of MIAs.

2. Materials and methods

This present retrospective study was approved by the medical ethics committee of our hospital. Written informed consent was obtained from all patients or from their first-degree relatives (if they are not neurologically intact) for publication of their cases and accompanying images.

Medical records were prospectively collected (all entrance data were collected at the time of hospitalization) from consecutive 409 cases of cerebral aneurysms which were treated surgically at Department of Neurosurgery of our hospital, between the years 2011 and 2013. Only the patients diagnosed as having multiple aneurysms and at least one of their aneurysms surgically treated were included in this study ($n = 90$). Clinical outcomes were evaluated using patients' complaints, locations, treatment choices, comorbidities, complications, mortality and morbidity rates. The clinical outcomes were evaluated using Glasgow Outcome Scale (GOS). Surgically treated patients underwent a craniotomy then microsurgical clipping of all aneurysms that had been accessed. The aneurysms not appropriate for clipping were wrapped by a thin layer of very small cotton pad, or sent to coiling/embolization.

Statistics below are expressed as the mean ± standard deviation values together with the range between parentheses. Differences among groups were assessed with the one-way analysis of variance (ANOVA) using the SPSS 21.0 statistical package. Significance in the multivariate model was determined by a $p < 0.05$, and a trend-level effect was assigned to a $p = 0.05–0.10$, all p values were given with odds ratio (OR).

2.1. Surgical procedure

First of all; brain computerized tomography (CT), cerebral angiogram, high-quality three-dimensional CT angiography (3-DCTA) and/or digital subtraction angiography (DSA) are well studied. Aneurysms' number, their projections, abnormal morphological changes, hypoplasic arteries and/or ruptured aneurysms are evaluated. According to all of these variants surgeon tries to understand the place and projection of ruptured aneurysms. The conditions where anatomy permits unilateral approaches should be assessed in detail and decided preoperatively, preferring ipsilateral approaches over bilateral approaches and single stage over multiple stages. Ruptured, irregularly shaped and large aneurysms (good candidates for rupturing) are first priority for repairing.

Craniotomy should always be performed on the side of the ruptured aneurysm. The desire to clip all the aneurysms must not put the patient in danger by starting from the non-ruptured site so as to facilitate the single stage clipping of all the pathology. After the bleeding aneurysm is dealt with, incidental one/s must come into light. The projection of contralateral or distal aneurysms, the depth required to reach the distal aneurysms and experience of the surgeon are other factors may play role in craniotomy place and size.

Under general anesthesia the patients are positioned supine with the head held in fixation device after slightly extended the malar eminence to be uppermost. The head generally turn to the opposite side in 45 degree and tilted the same amount. This will facilitate the exposure of the Sylvian fissure and especially help exposing of the aneurysms on the contralateral side by allowing the contralateral A1 and M1 to line up and be seen as a near-straight path flowing distally. In this series, the neurosurgeon used lateral supraorbital craniotomy for all aneurysms about 3-cm to 3-cm in size that are planned for single stage clipping, except for additional pericallosal and/or callosomarginally situated ones which are dealt with a slightly larger but single craniotomy extending medially stopping in the immediate midline to be able to visualize interhemispheric fissure. The appropriate basilar tip aneurysms are of no exception. Basillary trunk and/or other posterior system aneurysms are not considered to be appropriate for single stage intervention together with anterior system aneurysms.

After suitable craniotomy is performed the roof and the lateral walls of the orbit are radically thinned to a near total, and the sphenoid ridge is drilled to allow an extra space for exposure. Thin drilling is of utmost importance; taking away a non-neuronal, non-functional, view-limiting bone gives the surgeon nearly double the space he would otherwise have to work in. In the presence of ipsilateral proximal carotid aneurysms, the anterior clinoid process may be removed before opening the dura mater for a safer go-ahead. Drilling is performed using a 5-mm burr of high-speed drills with profuse irrigation. A 3-mm diamond drill is used only when anterior clinoid process or optic canal is being drilled. Removing bone adequately will minimize retraction so as to limit using retractors. In our series, we never ever use self-retaining retractors which put the brain under continuous pressure and leading to inevitable direct or venous-flow-obstruction infarcts. The suction retraction, always used thru a thin cotonoid applied to brain, is a wonderful way of exposure that allows the brain to breathe whenever the surgeon is tired of pulling and releases his hand. Fibrillary surgical is applied in between the cotton pad and the brain to avoid sticking of the cotton to the brain and resulting in contusion of the cortex when removing the cotton in the end of the operation.

The Sylvian fissure is never opened; this is found to be extremely helpful in avoiding unnecessary arterial manipulations. If it is a middle cerebral artery (MCA) aneurysm, the Sylvian is opened just over the dome and then proximal and distal ends revealed. Further splitting of the fissure up till carotid artery was never necessary. Arachnoid knife (beaver blade) is important to allow dissecting aneurysm and surroundings with minimal trauma to surrounding neural and vascular structures. In case of anterior communicating artery aneurysm, frontal lobe on the same side is extensively freed of adhesions to anterior fossa, optic nerve and dural attachments to allow 'falling down' of the lobe to gain more space and avoid retraction. If the case involves aneurysms on the other side, contralateral frontal lobe and temporal lobe is also extensively freed of arachnoid adhesions to the adjacent bone neighboring dural layer which will enormously increase the space to operate, decreasing the need to manipulate the brain, which is a priority in any surgery.

Bolus mannitol infusion of 8–12 mg/kg, roughly 60 mg, that is 300 cc of 20% mannitol is started just prior to incision, again to gain space, facilitating the surgery. In fact, many times safe surgery will only be possible after shrugging the brain by mannitol. Dexamethasone is also a good tool to get the brain smaller prior to starting the surgery. Lamina terminalis is opened in all our cases with SAH before starting aneurysm dissection for further brain relaxation and space gaining, and to avoid hydrocephalus that may occur secondary to SAH. For non-ruptured aneurysms as cisternal CSF draining is satisfactory, post clipping opening of lamina terminalis is preferred. This also avoids unnecessary oozing into the third ventricle during dissection.

Gyrus rectus resection may be required to fully expose the aneurysm neck and vascular complex in anterior communicating artery aneurysms. This is a face saving solution if the anterior communicating artery is not exposed by the above methods. This will avoid too much retraction and save valuable brain tissue not meant to disturb. When gyrus rectus resection is necessary, extreme caution must be exercised to not advancing into the counter-lateral gyrus rectus as this will result in unbearable memory complications.

The ruptured aneurysms should be exposed and clipped first. In unruptured multiple aneurysms or the rupture side is uncertain, aneurysms should be clipped in a retrograde model, starting from the most distal one to superficial. When unruptured aneurysms of the 'other side' are difficult to reach, a contralateral suitable craniotomy is recommended at the same operation or at later séance. Applying of temporary clips is a good way to facilitate permanent clip insertion (maximum 3 min). Intraoperative micro-Doppler probe was useful in many cases. After clipping is completed the dome is always punctured with a needle to see the exclusion of the dome from the circulation. Papaverine is added to rinsing water from the very beginning of the operation. After clipping papaverine is applied to the exposed arteries. Microsurgical clipping of all reachable aneurysms was performed. The aneurysms which were not appropriate for clipping were wrapped with very thin cotton prepared like a moocher to facilitate fibrosis. Some are sent to endovascular treatment if not clippable.

2.2. *Illustrative cases*

Case 1: A 61-year-old female patient presented to our emergency department of neurosurgery with severe headache followed by nausea and vomiting. Exception for she was hypertensive patient on medication, there was no known further significant diseases in her past medical history.

On examination, patient was well oriented, afebrile and vital parameters including blood pressure were normal. There was no motor or sensory loss. Pupils were normal in size and reacting normally to light. Nuchal rigidity was two positive. There was no neurological deficit apart from rigidity. Rest of the systemic examination was unremarkable. The patient was evaluated as Hunt–Hess grade 2.

The patient was referred to the radiology department for further evaluation after suspicion of SAH; cranial CT showed SAH that is evaluated as grade 4 in Fisher scale and mild hydrocephalus (Figure 1). DSA was performed and multiple aneurysms of bilateral MCA, anterior communicating (ACoA) and basilar arteries were detected (Figure 2).

The patient underwent microsurgical clipping operation using left lateral supraorbital craniotomy approach all aneurysms were clipped. No blood transfusion was needed. The patient had no neurological deficits after microsurgical clipping treatment. Postoperative CT (Figure 3) and DSA (Figure 4) were performed. She recovered good and discharged after 7 days without any complication. The patient on her postoperative 48th month doctor-visit was doing well.

Case 2: A 38-year-old female patient presented to our outpatient clinic of neurosurgery with headache for more than 2 years. The last three months she was experiencing fatigue after mild or moderate efforts. No known further significant diseases in her past medical history.

On examination, patient was well oriented, afebrile and vital parameters including blood pressure were normal. There was no motor or sensory loss. Pupils were normal in size and reacting normally to light. Nuchal rigidity was absent. There was no neurological deficit apart from rigidity. Rest of the systemic examination was unremarkable.

Cranial MRI showed bilateral MCA aneurysms (Figure 5). DSA was performed and aneurysms of bilateral MCA were

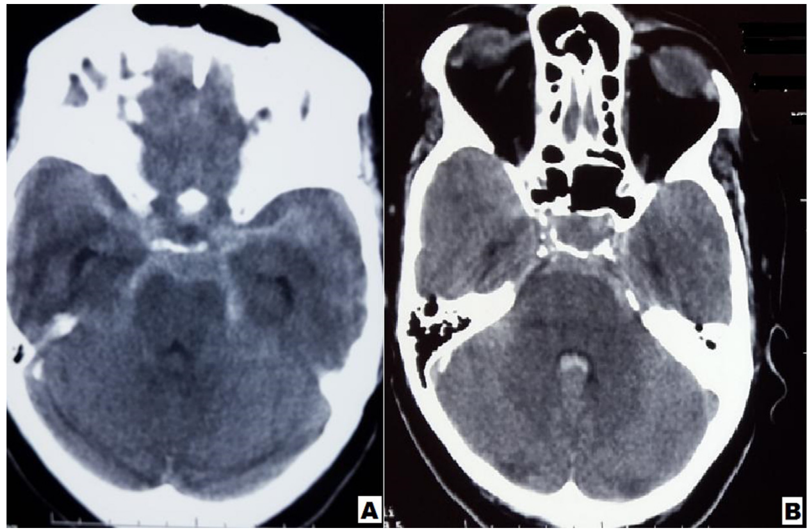

Fig. 1 – Preoperative cranial computerized tomography (CT) revealed on subarachnoid hemorrhage (SAH) that evaluated as grade 4 in Fisher scale and mild hydrocephalus. (A) Perimesencephalic SAH and mild hydrocephalus is appearing in temporal horns of lateral ventricle. (B) intraventricular hemorrhage in fourth ventricle, i.e. that is Fisher grade IV SAH.

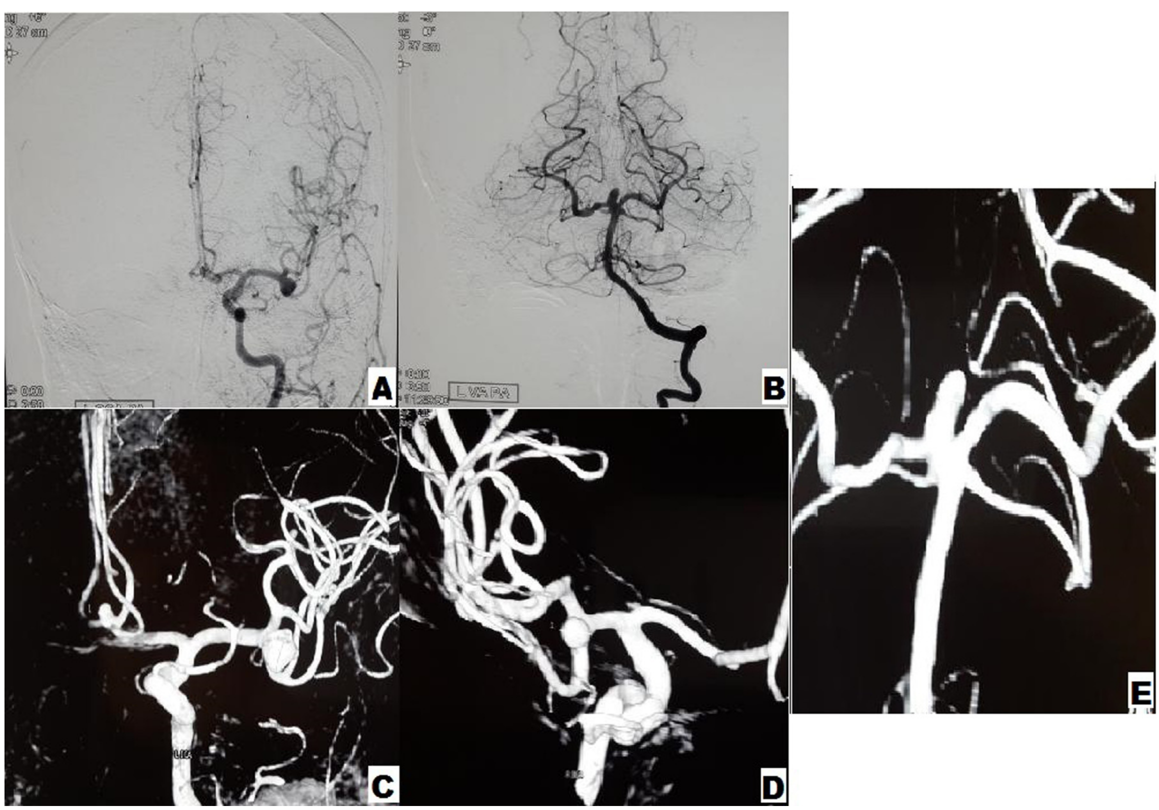

Fig. 2 – Preoperative DSA shows multiple aneurysms of bilateral middle cerebral, anterior communicating and basilar arteries. (A) Preoperative DSA shows left MCA aneurysm. (B) Preoperative DSA shows basilar artery aneurysm. (C) Preoperative three-dimensional DSA shows both of left MCA and ACoA aneurysms. (D) Preoperative three-dimensional DSA shows both of right MCA and ACoA aneurysms. (E) Preoperative three-dimensional DSA shows basilar artery aneurysm.

confirmed (Figure 6). The patient underwent micro-surgical clipping operation using right lateral supraorbital craniotomy approach both aneurysms were clipped. Postoperative DSA was performed (Figure 7). The patient had no neurological deficits after microsurgical clipping treatment. She recovered good and discharged after 4 days without any complication. The patient on her postoperative 60th month doctor-visit was doing well.

Fig. 3 – Postoperative cranial CT shows that all four aneurysms were clipped.

3. Results

221 aneurysms were detected in 90 (49 female, 41 male) patients. The mean age was 50.8 ± 11.9 (25–82) years. There were 67 patients presented with SAH, while 23 patients were diagnosed incidentally as unruptured aneurysms. Sixty-five patients (72.2%) were presented with 2 aneurysms (2 out of them presented after 9 and 10 years as single aneurysm), seventeen patients (18.9%) were presented with three aneurysms, whereas eight patients (8.9%) were presented with four or more aneurysms (Table 1). The most common complaint was severe headache (94%) in SAH group and migraine type headache (60.8%) in unruptured aneurysm group (Table 2). According to location of the arteries; ACoA (n = 50), MCA [n = 94 (right: 49, left: 45)], internal carotid artery [n = 49 (right: 34, left: 15)], posterior communicating artery [n = 13 (right: 9, left: 4)], anterior cerebral artery [n = 10 (right: 6, left: 4)], basilar artery (n = 3) and superior cerebellar artery (n = 2). According to Hunt–Hess scale of SAH group (grade 1: 8), (grade 2: 35), (grade 3: 13), (grade 4: 7), and (grade 5: 4). According to Fisher grade; (grade 1: 0), (grade 2: 7), (grade 3: 35), and (grade 4: 25). The most comorbidities of SAH patients were smoking and hypertension which seen in 43.3% out of them (n = 29) for each. However, the most comorbidity of unruptured aneurysms was hypertension which seen in 47.8% (n = 11) out of them (Table 3). Observation was the choice of treatment in 1.4% (n = 3) out of all aneurysms (there were 2 aneurysms could not be treated because of the

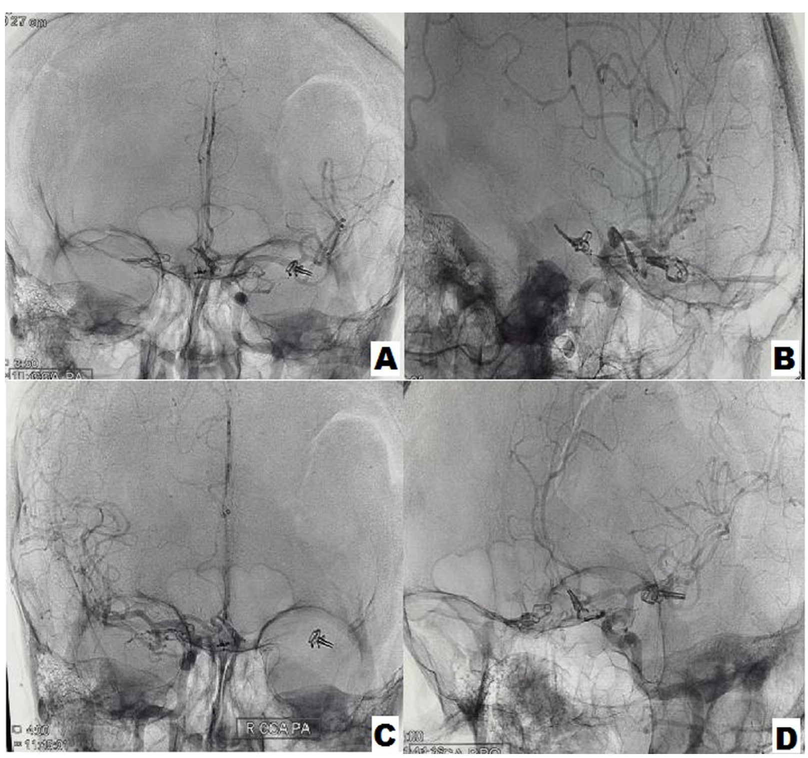

Fig. 4 – Early postoperative DSA demonstrates that all four aneurysms were clipped without rest. (A) and (C) Anteroposterior aspect of early postoperative DSA demonstrates that all aneurysms were clipped without rest (A) DSA was obtained from left common carotid artery (CCA). (C) DSA was obtained from right CCA. (B) and (D) Lateral aspect of early postoperative DSA demonstrates that all aneurysms were clipped without rest (B) DSA was obtained from left common carotid artery (CCA). (D) DSA was obtained from right CCA.

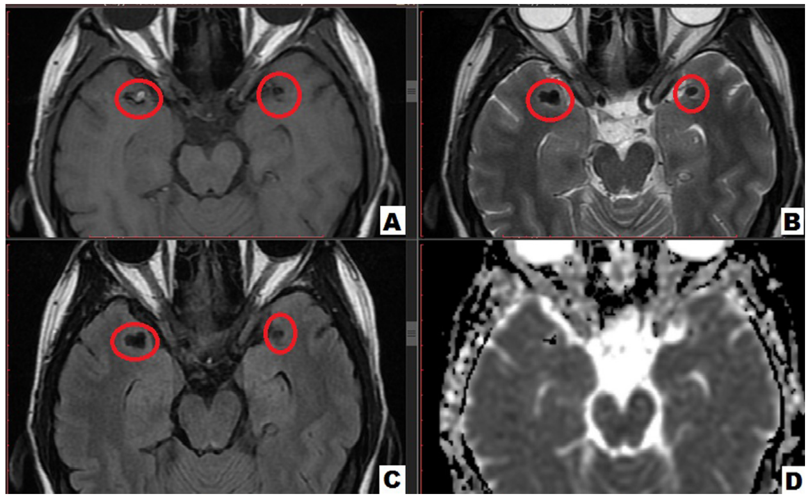

Fig. 5 – Preoperative magnetic resonance images (MRI) revealed on bilateral middle cerebral arteries' aneurysms. The red cycles indicate to the aneurysms. (A) T1-weighted MRI; (B) T2-weighted MRI; (C) T2-flair-weighted MRI; and (D) apparent diffusion coefficient (ADC). (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

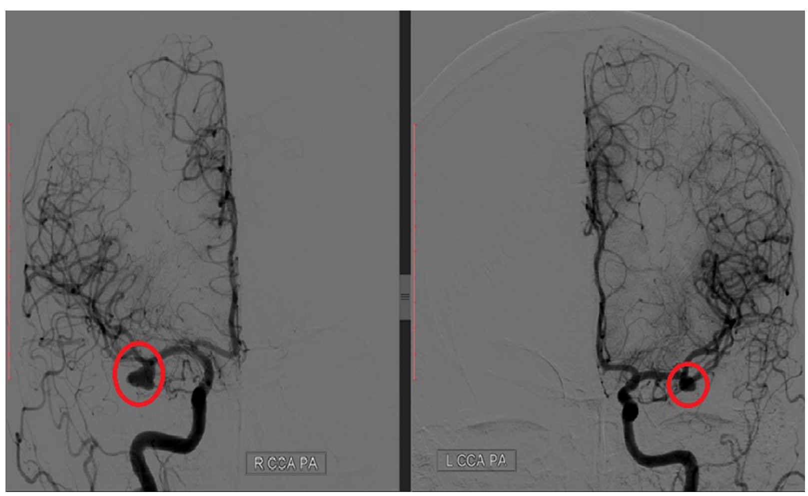

Fig. 6 – Preoperative DSA shows multiple aneurysms of bilateral middle cerebral. The red cycles indicate to the aneurysms. [Right side] Preoperative DSA shows right MCA aneurysm. [Left side] Preoperative DSA shows left MCA aneurysm.

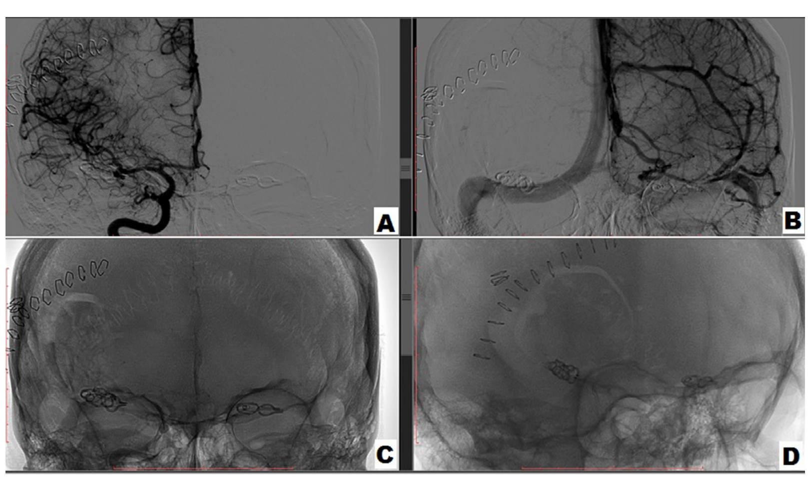

Fig. 7 – Early postoperative DSA demonstrates that all four aneurysms were clipped without rest. (A) Coronal aspect: Rt. MCA aneurysm was clipped. (B) Coronal aspect: Lt. MCA aneurysm was clipped. (C) Anteroposterior aspect. (D) Lateral aspect.

Table 1 – Numbers of aneurysms in each patient.

Numbers of aneurysms	Ruptured aneurysms				Unruptured aneurysms			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
2	25	73.5	26	78.8	8	53.3	6	75.0
3	7	20.6	6	18.2	3	20.0	1	12.5
≥4	2	5.9	1	3.0	4	26.7	1	12.5
Total	34	100.0	33	100.0	15	100.0	8	100.0

Table 2 – Baseline clinical and demographic characteristics of the 90 patients.

	Ruptured aneurysms	Unruptured aneurysms	All Pts
Age (years)	50.5 ± 13.2 (25–82)	51.4 ± 7.4 (37–64)	50.8 ± 11.9 (25–82)
No. of patients	49 pts (57.1%)	41 pts (42.9%)	90 pts (100%)
Gender (F/M)	34/33	15/8	49/41
Compliants – headache	[Severe] 94% (64/67)	[Chronic] 60.8% (14/23)	86.7% (78/90)
- Nausea ± vomiting	52.2% (35/67)	13% (3/23)	42.2% (38/90)
- Impaired consciousness	40.3% (27/67)	0	30% (27/90)
- Vertigo	1.5% (1/67)	43.5% (10/23)	12.2% (11/90)
- Generalized seizure	10.4% (7/67)	4.3% (1/23)	8.9% (8/90)
- Hemiparesis	4.5% (3/67)	8.7% (2/23)	5.6% (5/90)
- Memory impairment	0	17.4% (4/23)	4.4% (4/90)
- Neck pain	4.5% (3/67)	0	3.3% (3/90)
- Aphasia/dysphasia	3% (2/67)	0	2.2% (2/90)
- Behavioral impairment	1.5% (1/67)	0	1.1% (1/90)
- Fatigue	0	4.3% (1/23)	1.1% (1/90)
Follow-up period[a] (months)	30–173 (Av. 54.8 ± 23.4)	30–63 (Av. 44.3 ± 10.1)	30–173 (Av. 52.3 ± 21.3)
Mean length of hospital stay (days)	11.1 ± 8.0 (4–39)	7.2 ± 3.5 (3–16)	10.2 ± 7.4 (3–39)

[a] Follow-up periods were calculated only for patients who are still alive after treatment; pts: patients.

Table 3 – Co-morbidities of the 90 patients.

Co-morbidities	Ruptured aneurysms				Unruptured aneurysms			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
Smoking	11	32.6	18	54.5	4	26.7	1	12.5
Hypertension	20	58.8	9	27.3	9	60.0	2	25.0
Coronary artery diseases	6	17.6	1	3.0	0	0	2	25.0
Diabetes mellitus	3	8.8	1	3.0	0	0	1	12.5
COPD[a]	2	5.9	2	6.1	0	0	2	25.0
Thyroid dysfunction	2	5.9	0	0	3	20.0	1	12.5
CVA[b]	1	2.9	1	3.0	1	6.6	1	12.5

[a] COPD: chronic obstructive pulmonary diseases.
[b] CVA: cerebrovascular accident.

Table 4 – Treatment modalities performed for MIAs in our 90 patients.

Treatment modalities	Number of aneurysms		Number of patients	
	N	%	N	%
One craniotomy for ipsilateral aneurysms	134	60.6	66	73.3
One craniotomy for both side aneurysms	33	15.0	11	12.2
Two craniotomies at two stages	27	12.2	10	11.1
Two craniotomies at same stage	12	5.4	3	3.3
Wrapping	5	2.3	5[a]	5.6
Embolization/coiling	5	2.3	5[a]	5.6
Observation	3	1.4	3[a]	3.3
No treatment	2	0.9	2[b]	2.2

[a] These patients were treated as one of previous modalities.
[b] These patients were treated for two ruptured aneurysms and followed up in neurosurgical ICU because of their worse neurological presentation GSC < 8. Both of them were lost.

2 patients who were died latter). Embolization/coiling was the choice of treatment in 2.3% ($n = 5$) out of all aneurysms. Wrapping using muscles was carried out in 2.3% of aneurysms ($n = 5$). Twelve aneurysms (5.4%) which detected in three patients were treated using two craniotomies that were performed at same stage. These patients were involved with 2, 4 and 6 aneurysms; respectively. Twenty-seven aneurysms (12.2%) out of all aneurysms which were detected in ten patients were preferred to clip on two stages. Thirty-three aneurysms (15%) were treated at the same stage in eleven patients (Table 4). All thirty-three aneurysms were clipped microsurgically. Fifteen out of these thirty-three aneurysms were clipped contralaterally (Table 5). 134 aneurysms (60.6%) which were detected in 66 patients were clipped microsurgically. Three patients presented again as SAH originating from another aneurysm that was not visible in DSA performed

Table 5 – Baseline clinical, demographic characteristics and surgical outcomes of the 11 patients who treated contralaterally at the same stage.

No	Gender	Age	SAH[a]	Location and numbers	Outcome	PO stay[b]
1.	Female	57	No	ACoA (2); L.ACAʹ; R.MCA[4]	Motor deficit	14
2.	Female	36	Yes	Bil. MCAʹ; ACoA [3]	Recovered; seizure	17
3.	Female	37	No	R.MCA; R.ICA; L.ICAʹ [3]	Recovered	7
4.[d]	Female	38	No	Bil. MCAʹ [2]	Recovered	4
5.	Female	73	No	R.ICA-Paraophthal; L.PcoAʹ [2]	Recovered[c]	8
6.	Female	56	No	Bil. MCAʹ; ACoAʹ; R.ICA [4]	Recovered	7
7.	Male	25	Yes	L.MCAʹ (2); R.ACA [3]	Recovered	5
8.	Female	42	No	Bil. MCAʹ; L.PCoAʹ [3]	Recovered	4
9.[f]	Female	61	Yes	Bil. MCAʹ; Basilar; ACoA [4]	Recovered	7
10.	Male	49	Yes	Bil. ACA-Pericallʹ; L.MCAʹ [3]	Recovered	6
11.	Female	46	Yes	Bil. ICA biff. ʹ [2]	Died[e]	38

Notes: All thirty-three aneurysms were clipped microsurgically at the same stage. Fifteen out of these thirty-three aneurysms were clipped contralaterally (from the opposite side craniotomies) where indicated with (ʹ). In cases number 1–8, 10 and 11, the craniotomies were in right side. In case number 9 craniotomy was in left side. Bil: bilateral.

[a] Presentation as SAH or not.

[b] Postoperative hospital length stay periods are given by days.

[c] This patient was involved with transit dysarthria for 3 days and recovered before she was discharged.

[d] This is the illustrative case 1 which is given in the manuscript.

[e] This patient was doing well after surgery till postoperative 7th day when she involved with pneumonia then transferred to ICU where was died after one month.

[f] This is the illustrative case 2 which is given in the manuscript.

after first time bleeding; 122, 106 and 23 months after curative treatment. Association with intracranial arteriovenous malformations was detected in two patients (2.2% of all MIAs in this series) who presented as SAH. Cigarette smoking is an independent risk factor for presentation as SAH, but only with trend-level significance (OR 2.75, $p = 0.053$). However, in the multivariate models only smoking when associated with male gender together are risk factors for presentation as SAH (OR 8.4, $p = 0.037$). Mortality rate was 13.3% ($n = 12$). Morbidity rate was 18.8% ($n = 17$), seven of those seventeen patients were partially or completely dependent on others for daily living activities before surgery (GOS ≤ 3). 67.8% ($n = 61$) of the patients were returned to normal their job and daily activities (GOS ≥ 4) at their last follow-up (52.3 months on average). The complications were hydrocephalus ($n = 9$), hematoma ($n = 2$), cerebrospinal fluid leakage ($n = 2$), infarction due to permanent vasospasm ($n = 2$), seizures ($n = 2$), surgical site infection ($n = 1$), rhinorrhoea ($n = 1$) and osteomyelitis ($n = 1$).

4. Discussion

The incidence of multiple cerebral aneurysms (MIAs) among patients who are diagnosed with aneurysm is 15–45% in the literature [2,9]. MIAs are observed in a fifth to a third of all cases of intracranially located aneurysms [7,10]. The prognosis of aneurysmal SAH has remained a serious medical challenge largely unaffected by the improvement in medical and microneurosurgical treatment modalities. The female preponderance in patients with MIAs is well-established observation in most previously published papers [1,2,4,5]. SAH and unruptured intracranial aneurysms are more common in females than in males [1,4]. In this series, the female predominance is observed in 54.4% of patients (Table 1).

Several studies showed that MIAs are associated with a less favorable outcome than are single aneurysm cases after SAH [2,8]. In this study, at their last follow-up, which is on average 52.3 months, 67.8% of patients have good outcomes and they returned to normal their job and daily activities (GOS ≥ 4). This is close to the experience of all 409 (319 involved with single aneurysm and 90 involved with MIAs) patients that were underwent surgical treatment for single aneurysms in the same period and institute. Out of 319 patients 241 recovered fully, 49 are experienced one or more deficits/morbidities and 29 are dead. For morbidity rate and mortality rate (OR 1.03, $p = 0.54$) and (OR 0.43, $p = 0.012$). The difference though is not significantly different.

In this series, treatment options were widely varied from observation to microsurgical clipping. Observation was the choice of treatment for small regular aneurysms ($n = 3$). These patients were close controlled using cranial MRI angiography and only one baby aneurysm was enlarged in diameter from 2 mm × 1 mm to 3 mm × 2 mm but it is still regular in shape and the patient's age of 76 years and he is still on follow-up list. When an unruptured aneurysm is detected, the risk of rupture has to be balanced against the risks of preventive treatment. However, assessment of rupture risk is not easy. In recent two studies, one of them was pooled analysis of individual patient data from six prospective cohort studies, predictors of rupture were including geographical region, hypertension, age, history of SAH from another aneurysm, aneurysm size and location, aneurysms with large diameter (>7 mm) and aneurysms in the vertebrobasilar, anterior communicating, and posterior communicating arteries [5,11]. Such kind of aneurysms is carrying the highest risk of rupture.

Independent risk factors for recurrent SAH in one study were current smoking, younger age, and multiple aneurysms at the time of the initial SAH [12]. Hypertension was an additional important risk factor for aneurysm regrowth or de novo aneurysm formation in another retrospective study [13]. Cigarette smoking and hypertension are also established risk factors for both unruptured intracranial aneurysms and aneurysmal subarachnoid hemorrhage. Three patients presented again as SAH originating from another aneurysm that was not visible in DSA performed after first time bleeding; 122, 106 and 23 months after curative treatment. These (2 male and 1 female) patients are hypertensive and heavy smokers (smoke > 40 cigarettes/day). Despite this is small number (3 patients of 67) to make generalization but it is support that MIAs, hypertension, smoking and the presentation as SAH are risk factors to recurrent SAH or get new aneurysms.

The authors here tried to compare their experience when they treated MIAs contralaterally in eleven patients and when they treated patients with other options ($n = 79$). The mortality rates of both groups are 9.1% (for contralateral group) and 13.9% (OR 0.590; $p = 0.534$). The morbidity rates of both groups are 20% (for contralateral group) and 22.1% (OR 0.883; $p = 0.624$). The average of postoperative hospital length stay periods of both groups are 10.6 ± 9.9 days (for contralateral group) and 10.3 ± 7.9 days (OR 1.06; $p = 0.589$). The difference though is not significantly different. Therefore, surgical approaches do not show any superiority from each other in surgery-related complications.

In this study, the authors tried to understand the impaction of gender and comorbidities on presentation as SAH (Table 3). Despite female patients among those presented as SAH is nearly equal to the male patients as 34:33, 15 females to 8 male patients presented as unruptured aneurysms. The difference though is not significantly different (OR 1.82; $p = 0.17$). Male gender does not show any superiority from female to present as SAH.

In through review of the literature, the authors find out independent modifiable risk factors for SAH seem to be only cigarette smoking, alcohol consumption and hypertension. Smoking is the most important an independent risk factor for SAH which has already been proved in several cohort and case –control studies all over the world [14–19]. In North America and Europe, the prevalence of smoking in SAH patients ranges from 45 to 75% whereas in the general adult population it is 20–35%. Of SAH cases, 40% can be attributed to cigarette smoking [14,16–18]. In the current study, cigarette smoking is an independent risk factor for presentation as SAH, but only with trend-level significance (OR 2.75, $p = 0.053$). However, in the multivariate models only smoking when associated with male gender together are risk factors for presentation as SAH (OR 8.4, $p = 0.037$). In contrary, the thyroid dysfunction (hypothyroidism) is preventing factor for SAH in the patients involved with MIAs (OR 0.15, $p = 0.035$). On the other hand, OR and p values are calculated for other co-morbidities; hypertension, diabetes mellitus, coronary artery diseases, chronic obstructive pulmonary diseases, and cerebral vascular accidents [(OR 0.83; $p = 0.44$); (OR 1.4; $p = 0.62$); (OR 1.23; $p = 0.58$); (OR 0.67; $p = 0.48$); and (OR 0.32; $p = 0.27$)]. The differences though are not significantly different. Presence of any of these five comorbidities does not increase the risk of SAH presentation in MIAs' patients.

5. Conclusion

MIAs are not associated with a less favorable outcome than are single aneurysm cases when operated in single séance. We prefer microsurgical clipping of all the aneurysms in one stage if the aneurysm location is reachable. Combination of treatment options may be the choice of the treatment. Contralateral microsurgical clipping does not increase the mortality or morbidity rates. Thus, a single intervention definitely benefits the patient by halving the surgical risk and psychological trauma of being reoperated and saves precious health care time.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

References

[1] Ajiboye N, Chalouchi N, Strake RM, Zanaty M, Bell R. Unruptured cerebral aneurysms: evaluation and management (review article). Sci World J 2015;2015. Article ID 954954.

[2] Kaminogo M, Yonekura M, Shibata S. Incidence and outcome of multiple intracranial aneurysms in a defined population. Stroke 2003;34:16–21.

[3] Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8(7):635–42.

[4] Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. Neurology 2013;80(23):2154–65.

[5] Backes D, Vergouwen MD, Velthuis BK, van der Schaaf IC, Bor AS, Algra A, et al. Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms. Stroke 2014;45(5):1299–303.

[6] Jeon HJ, Lee JW, Kim SY, Park KY, Huh SK. Morphological parameters related to ruptured aneurysm in the patient with multiple cerebral aneurysms (clinical investigation). Neurol Res 2014;36(12):1056–62.

[7] Juvela S. Risk factors for multiple intracranial aneurysms. Stroke 2000;31:392–7.

[8] Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Management outcome for multiple intracranial aneurysms. Neurosurgery 1995;36:31–8.

[9] Rinne J, Hernesniemi J, Puranen M, Saari T. Multiple intracranial aneurysms in a defined population: prospective angiographic and clinical study. Neurosurgery 1994;35(5):803–8.

[10] Ellamushi HE, Grieve JP, Jager HR, Kitchen ND. Risk factors for the formation of multiple intracranial aneurysms. J Neurosurg 2001;94:728–32.

[11] Greving JP, Wermer MJ, Brown Jr RD, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol 2014;13(1):59–66.

[12] Wermer MJ, Greebe P, Algra P, Rinkel GJ. Incidence of recurrent subarachnoid hemorrhage after clipping for ruptured intracranial aneurysms. Stroke 2005;36(11):2394–9.

[13] Wermer MJH, vander Schaaf IC, Velthuis BK, Algra A, Buskens E, Rinkel GJE. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of exiting aneurysms. Brain 2005;128:2421–9.
[14] Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case–control study. Stroke 1986;17:831–5.
[15] Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005;36:2773–80.
[16] Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke 1993;24:639–46.
[17] Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002;33:1321–6.
[18] Longstreth Jr WT, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke 1992;23:1242–9.
[19] Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 2013;35:93–112.