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Management of Unbled Brain Arteriovenous Malformation Study

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Synopsis

In a recently-reported NINDS-funded randomized clinical trial, the first for brain arteriovenous malformations, limited to those discovered not having bled, medical management alone was found superior to medical management plus intervention to eradicate brain arteriovenous malformations. The trial was halted at the recommendation of the NINDS-appointed Data and Safety Management Board after 226 randomizations and a mean follow-up of 3.3 years due to a disparity favoring the medical arm (HR=3.41 95%CI: 1.72-6.76). Patients eligible for the trial were selected by the interventional teams as suitable for lesion eradication. The initial sample size of 800 and follow-up plans for mean 7 years were lowered and shortened, respectively, by the outcome data. An application for extended follow-up was given poor priority scores by a NINDS Study Section and Council due to estimations the disparities in outcomes would not change significantly.

Keywords

Arteriovenous malformation; Non-hemorrhagic presentation; Randomized Clinical Trial; Interventional Management; Medical Management

Introduction

Incidence

In the Cooperative Study of Subarachnoid Hemorrhage, still the largest such series to date, symptomatic AVMs were found in 549 of 6,368 cases, representing an incidence of 8.6% of subarachnoid hemorrhages.¹ Since subarachnoid hemorrhage accounts for roughly 10% of strokes, AVMs make up approximately 1% of all stroke, 1.8% in an eligible population of 100,000 studied over a period of 3 years%²

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Prevalence

Data on prevalence of AVMs is difficult to obtain. The early autopsy studies suggested a prevalence of 4.3%.³ Non-invasive brain imaging has created an increased awareness of AVMs over the past few decades. The New York Island Study of a population approximating the 10 million living in Manhattan, Staten Island, Brooklyn, Queens, and Nassau and Suffolk Counties documented 1.34 per 100,000 person-years (95% CI, 1.18 to 1.49). Hemorrhage is the presenting feature in 0.68 per 100,000 (95% CI, 0.57 to 0.79).⁴ Similar data was published from the population-based Scottish Vascular Malformation Study.⁵

Vascular features

AVMs are a coiled mass of arteries and veins partially separated by thin islands of sclerotic tissue, lying in a bed formed by displacement rather than invasion of normal brain tissue.³ Long considered congenital, recent reports document de-novo cases.⁶ It remains unknown which ones continue to develop and which ones are status anomalies. No method has been generally agreed on for defining the epicenter of an AVM.⁷ There is no special predilection for AVMs in any part of the brain, the locations reflecting the relative volume of the brain represented by a given region.⁶ Location appears to have no bearing on the tendency for hemorrhage, growth, regression, vascular complexity, or size. The vast majority of AVMs are single, but noninvasive imaging has increased the number of multiple AVMs, one series citing 9%.⁸ When multiple, the lesions are usually small. Growth, stability, and even regression has been documented.⁹⁻¹¹

Natural History

Prior to modern imaging, so few cases were discovered incidental to formal angiogram that no useful prognostic data existed. Early estimates of the annual morbidity and mortality of brain arteriovenous malformations (bAVMs) came from large referral institutions.¹²⁻¹⁴ Review of these classic works, whose case material is based mainly on angiographic studies, suggest their estimates of hemorrhage incidence, morbidity and mortality, were drawn largely from those who came to clinical attention from the subset of the population at the highest risk for haemorrhage, and they did not discover the larger subpopulation of those unaffected or suffering only minor syndromes from hemorrhage.

Ignorance of the natural history of bAVMs has long confounded pre-trial center-based registry data. The widely cited 1990 publication entitled "The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment" was a case series of bAVMs discovered over a period from 1942-1975. It cited annual hemorrhage rates as high as 4% and mortality 1%.¹⁴ The authors pointed out that the majority of the patients (160 of 242) had bled. A surviving co-author commented privately that these cases were considered too daunting for attempted surgical removal. These data may well apply to their cohort but provides little insight into the true natural history for those discovered with no prior hemorrhage, and who are to be followed for annual status with no plan for intervention unless hemorrhage occurs. Even the most recent meta-analyses have been confounded by the inability to segregate those bled from those not, leaving unclear whether the wide range of adverse outcomes from attempts at eradication applies

equally to the two groups.¹⁵ Few reports have made reference to the treatment outcome segregating with or without pre-treatment hemorrhage.^{16, 17, 18} The difficulties demonstrating the value of intervention in unbled bAVMs prompted the suggestion such therapy was experimental, despite its being well established.¹⁹

These percentages have long been used since then as a basis for treatment to prevent rehemorrhage, even to prevent initial hemorrhage. Although the most commonly cited “natural history” publication reported relatively high hemorrhage rates, some reports from small populations have documented rates even higher.^{20, 21} Acting on such presumed natural history, young individuals were (and some still are) told that they have a 40% to 50% risk of some major incapacitating or fatal hemorrhage from an AVM in their projected life span. This projection is often made regardless of whether the patient presents with seizure, migraine, unrelated symptoms, or due to discovery of the bAVM for brain imaging done in pursuit of another diagnosis.

Modern assessments, using non-invasive imaging, have reported much lower rates for those discovered not having bled, some as low as 1% per year.^{22, 23, 23, 24} Data drawn from a population of almost 9 million persons living in Manhattan, Staten, and Long Island in 2001-2004⁴ have also modified downward estimates for both initial morbidity and mortality.^{4, 24, 25, 26} Similar findings were reported from the Scottish Vascular Malformation Study⁵ and replicated in recent meta-analyses.²⁷ These studies challenged the basis for intervention in unruptured bAVMs. They were the basis for application for a randomized clinical trial comparing outcome for those discovered unbled and treated only medically versus those treated medically and also by intervention to eradicate the bAVM.

Clinical Presentations—*Hemorrhage* is the presenting complaint in approximately half of the cases.²⁸ Primarily parenchymatous hemorrhage occurs most often (63% of cases). Primarily parenchymatous and associated subarachnoid hemorrhage occurs in 32%, and ventricular hemorrhage alone least often, at 6%.¹ For the hemorrhages limited to the parenchyma, the syndrome is a combination of the hemorrhage into the region of the bAVMs with secondary effect on adjacent parenchyma.²⁹ This secondary effect is often minor, with satisfactory remission of the syndrome.³⁰ The hemorrhage affecting the subarachnoid space usually involves the convexity, far less often the region of the base of the brain. Vasospasm is uncommon.³¹ Since many bAVMs drain to the ventricular wall, the effect of the hemorrhage may primarily be its venting into the ventricular space. A distinctive clinical feature of such ventricular hemorrhages is an unrelenting course over minutes from the onset of headache to stupor. The ventricular hemorrhage usually produces a hemo-hydrocephalus with limited parenchymal component. If severe, a ventricular drain can be used, but many are mild enough that such drainage can be avoided.

Headache is a presenting feature in 15% of bAVMs. In 1940, Northfield suggested recurrent unilateral headache could mean an underlying bAVM.³² No evidence was presented, but the idea continues to the present day. Headache is such a common complaint in the population at large, it has proved difficult to determine if the headache associated with AVMs is distinctive in any of its clinical features including location.^{2, 27, 32} Mackenzie emphasized the tendency of the headaches to occur before the aura and for the aura to persist beyond the

few minutes that typifies migraine, a finding not confirmed by others.³³ The literature remains limited: Lees had only three cases whose headache was ipsilateral to the AVM among the 11 headache cases in his series of 70 AVMs.³⁴ More recent authors claim a correlation between headache and AVMs,³⁵ including occipital location,³⁶ but others not.⁶

Seizures as the presenting complaint affect roughly a third of bAVMs. The prevalence is highest in those with bAVMs affecting the convexity.³⁷ Reports vary widely for severity, ease of control with medication, or prognosis for hemorrhage. Seizures are most frequent for bAVMs involving the surface of the brain, especially the centroparietal area.²⁸ but is unusual for deep AVMs. The type of seizure is often unreported but where described, focal spells predominate, varying from 45% to 59%.¹⁴ Hemorrhage from bAVM has been found to confer a higher risk for first-ever seizures compared with incidental bAVMs.³⁸ Seizures are not a prognostic factor for hemorrhage. Hemorrhage occurred within 1 year in only 15% of 90 cases of seizure in the Cooperative Study and their incidence or recurrence is not modified by intervention to eradicate the bAVM³⁹

Cerebral Steal: Roughly 6% have some focal neurological deficits of gradual onset. In most, the deficit is limited to the region of the brain served by the AVM. Early angiography showing the dense concentration of contrast flowing through the fistula and the comparatively thinner appearance of non-affected local vessels supported the idea there could be cerebral steal with ischemia.⁴⁰ The reported neurological syndromes have evolved over periods as short as 3 years or as long as 10 years, but with no sudden loss of function to suggest infarction and without obvious instances of hemorrhage. The inferred presence of steal was used to justify intervention to eradicate the bAVM. A publication challenging the role of cerebral steal was based on 32 cases with measurements of feeding arterial pressure showing no ischemic effects in peri-lesional vessel, and a clinical series of 152, with 13 focal neurological deficits unrelated to hemorrhage.⁴¹ Post publication, a single criticism was published,⁴² and cerebral steal reports in case series fell into the low single digits. However, neuropsychological impairments exist and can show improvement in the setting of dural fistulas.⁴³ Mass effects, mostly in brainstem bAVMs, apply in most of the cases.⁴⁴

Interventional Management

Center-based registry reports focused on outcomes from intervention have regularly provided demographics of those treated (e.g. age, gender, lesion size and location, and usually the percent of the cohort having had prior hemorrhage) but detailed the results of treatment without segregating the outcomes based on pre-treatment hemorrhage status.¹⁵ Investigators found it impossible to assess the extent to which the intervention created a clinical disturbance not present before, aggravated one already present, or had no such effects.⁴⁵ This publication tendency persists to the present day, despite the awareness a trial was comparing the outcomes for those bled or not bled. An overview of outcomes was reported in the largest meta-analysis to date.¹⁵ (See Figure 1)

Treatments to eradicate a brain AVM (bAVM) began with *surgery*. At first there were attempts to ligate feeding arteries, and in recent years, attempts at complete removal of the lesion. BAVMs are embedded in brain and often associated with deep draining veins,

making surgical removal among the most challenging of the neurosurgical procedures. Commonly cited risk factors for surgical eradication are <2% for mortality and 5% for significant morbidity, with 12% for minor morbidity following total obliteration of the lesion. Such rates apply mainly to those of small size (<3 cm), no deep venous drainage, and location away from functionally important brain areas, Grade I of VI on the Spetzler-Martin grading system.⁴⁶ Those of higher grade can be expected to show higher rates of adverse outcomes. A recent addition has been made to the Grading system.⁴⁷

In recent decades *embolization* has become popular. It was begun both in hopes of reducing the size of the bAVM to one suitable for surgery, and concerns for 'perfusion-pressure breakthrough' after feeding artery occlusion.⁴⁸ This latter issue was subsequently found related to cerebral hyperemia but not to feeding artery pressure.⁴⁹ Initial effort at embolization used small pellets of Silastic impregnated with barium and fragments of muscle removed from the adjacent sternocleidomastoid muscle, directly injected into the feeding arteries during open surgery.⁵⁰ The field rapidly developed toward trans femoral catheters delivering a variety of embolic materials, ranging from polyvinyl alcohol,⁵¹ low viscosity silicone rubber⁵² prothrombotic metal, N-butyl cyanoacrylate (NBCA) glues⁵³ and more recently ethylene vinyl alcohol (Onyx®).⁵⁴ None of these agents are free of risk, especially when the material deposits in the venous outflow before complete occlusion of the bAVM.⁵⁵ Guglielmi detachable coils are among the devices used.⁵⁶ Despite large cohorts from single centers, most reports do not cite outcomes for those not having bled prior to intervention,¹⁷ but some of the most recent have done so, noting non-hemorrhagic presentation as predictor for new deficits ($p<0.002$)⁵⁷

Not to be denied, *radiotherapy* has also provided a large experience,⁵⁸ and, as with the other modalities, with widely varying results.⁵⁹ Radiotherapy is becoming increasingly popular, given its apparent non-invasive qualities. Its use has been shown to obliterate some of the smaller lesions.⁶⁰ Higher doses were required for the larger lesions, with uncertainty of success and concern for radiation necrosis.^{61,62} Minakawa et al repeated the angiogram 5 to 28 years after first discovery or treatment in 20 patients, 16 of whom were untreated while the remaining were residual. The AVM was unchanged in eight, larger in four, smaller in four, and had disappeared in four. The AVMs that disappeared were relatively small and fed by a single feeder or a few feeders.⁶³ Meta-analyses have shown a wide range of outcomes, not segregated by nonhemorrhagic presentation¹⁵ A recent report of late follow-up from some centers has documented a rate for those with non-hemorrhagic presentation of 1.2% compared with 3.3% for those hemorrhagic.⁶⁴

Treatments may fall short of total obliteration of the AVM due to halt of the program. Once an AVM has been removed (as proved by postoperative angiography), recurrent hemorrhage presumably should not occur, but recurrence has been documented in a small literature.⁶⁵ There is no useful literature on the long-term outcome for those with incomplete removal of the bAVM^{23, 24}

The ARUBA trial

A Randomised trial of Unruptured Brain Arteriovenous malformations (**ARUBA**), funded by NINDS, was recently reported.⁶⁶ It was designed to establish whether, for those with a bAVM discovered not having bled, the long-term outcomes for medical management was comparable, inferior or superior to “interventional therapy”. The interventions were those in common practice: endovascular procedures, neurosurgery, or radiotherapy and could be used alone or in any combination. The interventional arm was considered the ‘standard therapy’ while the medical arm was the ‘experimental’ arm.

The trial was funded by NINDS in 2006; 66 centers world-wide agreed to participate. The trial recruited 226 patients from 39 active centers world-wide at a steady rate of 3 per month beginning in April 2007. At a preplanned meeting with investigators April 2013, the NINDS-selected DSMB recommended cessation of randomizations. This recommendation was based on their review of a pre-planned interim analysis that revealed patients assigned to receive interventional therapy were greater than 3 times more likely to experience a stroke or death during the follow up period than their counterparts (33 months on average, HR=3.41 95%CI: 1.72-6.76). When randomization was halted, 48% of the cohort were entirely asymptomatic, 62% had bAVM size <3 cm, 66% had superficial drainage, and 100% had a modified Rankin Score of 0-1 (48% were zero) [Figure 2].

The DSMB also recommended further follow-up for all participants to determine whether the disparities in stroke and death rates would change. The follow-up would assess whether such differences translated into clinically meaningful difference in long-term functional outcome. These points were the basis for the formal NINDS announcement, posted on their website on May 9, 2013 (http://www.ninds.nih.gov/news_and_events/news_articles/ARUBA_trial_results.htm). The results were presented at the 23rd annual European Stroke Conference (London, UK) and published in Lancet (epub November 2013 with formal publication February 2014).⁶⁷ Its major finding favored the medical arm in the analysis ‘as randomized’ and even more ‘as treated’. [Figure 3]

Criticisms of ARUBA and Responses

During the active phase of ARUBA a steady stream of criticisms was published^{68, 69} and rebutted.^{70, 71} After publication more criticisms appeared.^{72, 73, 74} Many criticisms were based on undocumented inferences of biased patient selection, low skills from participating centers, low participation from alleged major centers, uncommon choices for intervention, low enrollment compared with those screened, and lack of reporting on outcomes from those eligible but not randomized.

Each of the major criticisms has received public presentation or published response: The demographics of the population match those reported from defined major populations;⁷⁰ the distribution of Spetzler-Martin Grades was indeed biased, but towards the more easily treated;⁷⁵ the participating centers showed their qualifications by over 600 publications found in PubMed for the years 2000-2010. The choices for intervention correspond to those most often published from individual centers. The criticism that too few had only surgery⁷⁶ is rebutted by the lack of reference to surgery as a single treatment modality in the only

management algorithm published for those not having bled.⁷⁷ Surgery was a treatment plan for 21 of the 100 patients. [Figure 4] The fate of those eligible but not randomized remains unreported because no participating center responded to the offer of a registry for such patients. The widely claimed 4% participation infers that >1400 screened were all eligible, but all but 500 were ineligible due to prior hemorrhage or intervention, and the for those eligible among the 39 active centers the randomization rate was fully 61%. Criticisms of the lack of data on microhemorrhages in assessment of unbled bAVMs⁷⁸ cannot be answered because the 2012 date of publication on microhemorrhages as a risk factor for rupture precluded its inclusion in the formal protocol during the trial. Finally, the brief mean time of follow-up was the result of the halting of the randomization phase by the DSMB, not the plan of the investigators. However, based on the disparity in outcome events between the two arms in the trial, study statisticians calculated a range of 12-30 years might be needed for events in the medical arm to reach that of the interventional group, assuming no further events occur in the latter.⁷⁹ We offer no comment on a recent complaint that neurosurgeons are being referred fewer cases for neurovascular surgery, and for the inference that the large number of cases eligible but treated outside for a trial presumably had satisfactory results.⁸⁰

Subset results

Reluctant to report data from small subsets in our trial, we have recently responded to post-publication criticism that the reported stroke outcomes in the interventional arm might contain a large number of clinically minor events, e.g. headache with a positive MR. Such events would have been counted as stroke because of a new symptom was associated with a new infarct or hemorrhage documented by MR (ARUBA clinical protocol).⁶⁷ We agree a clear statement is needed on the functional effect of stroke outcomes. Analysis of the mRS status at the time of the outcome event showed mRS 2 for only two of the eight in the medical arm but 28 of 34 in the interventional arm.⁷⁵ Recalculation of the odds ratio between the two arms of the trial showed a further favorable shift in the direction of the medical arm in the 'as treated' when the outcomes were limited to those with mRS 2.

The Future

The current status of the data from ARUBA leaves unsettled both the long-term rate of hemorrhage and hemorrhage severity for those in the medical arm. The investigators, backed by the DSMB and the NINDS Clinical Notice, applied for continued follow-up of the ARUBA cohort but were denied funding. Among the comments from reviewers was the inference the data would change little in the coming 5 years.

A unique opportunity still exists to clarify the long-term risk and the severity of hemorrhage in this well-characterized cohort of unbled brain AVMs. The ARUBA study contains 500 cases eligible for the trial. All of them, randomized or not, are well-characterized, known to ARUBA centers, and presumably available for follow-up. Many active centers are continuing to contribute follow-up for randomized cases pro bono. Their access to their patients could also permit assessment of those newly-described potential risk factors for hemorrhage: silent intralesional microhemorrhage⁷⁸ and single draining vein status.⁸¹ An update of cost factors for invasive management could also be included.⁸²

The resultant data would be a modern epidemiological documentation of the prevalence of bAVMs and incidence data for adverse outcomes for several well-characterized populations. The emphasis on those discovered unbled would provide a benchmark against which presumable improvements in interventions for lesion eradication could be compared.

Clinically Efficacy of Therapeutic Interventions

In adult patients (≥ 18 years) with an unruptured brain arteriovenous malformation addition of interventional therapy (ie, neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination) to medical management alone (ie, pharmacological therapy for neurological symptoms as needed) is Probably harmful (Level of Clinical Efficacy 2-X, Level of Evidence T1)

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Key Points

- ARUBA is the only randomized clinical trial to date comparing medical only vs medical plus intervention limited to those patients deemed by participating centers suitable for attempted eradication.
- The death/stroke outcomes led to a recommendation from an NINDS-appointed Data and Safety Monitoring Board to halt the randomization phase due to superiority for the medical arm.
- The NINDS Study Section and Council decided against funding for further follow-up, citing the likelihood the disparities between the medical and interventional arms would persist for the planned additional 5 years of follow-up.

Van Beijnum et al Meta-analysis JAMA 2011			
Bled & Unbled Mixed Cohorts No separate outcomes for Unbled			
	# (%)	# [cohort]	Median %
Microsurg	Acute	33 [1655]	29 (1.5-54)
	Severe	24 [1252]	7.4 (0-40)
Radiosurg	Acute	33 [3290]	0 (0-16)
	Acute Severe	32 [2558]	0 (0-4.8)
	Late	63 [6914]	13 (0/63)
	Late Severe	35 [2862]	5.1 (0-21)
Emboliz	Acute	18 [1201]	25 (7/655)
	Severe	16 [818]	6.6 (0-28)

"...treatment of brain AVM remains associated with considerable risks and incomplete efficacy. Randomized controlled trials comparing different treatment modalities appear justified.

Figure 1.

Meta-analysis reported by Van Beijnum et al. JAMA

Note the analysis includes those with hemorrhagic and non-hemorrhagic presentation. The quote is from the article.

Figure 2.
ARUBA intention to treat analysis showing superiority of the medical arm.

Figure 3.

ARUBA “as treated” analysis. Those randomized to the medical arm who crossed over to intervention and experienced an event from intervention are counted in the interventional arm; those randomized to intervention who had outcome event before initiation of intervention are counted in the medical arm.

Figure 4.
Interventional management for the 100 randomized to ARUBA