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Intervention for A randomized trial of unruptured brain arteriovenous malformations (ARUBA) — Eligible patients: An evidence-based review

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ABSTRACT

While intervention for ruptured arteriovenous malformations (AVMs) of the brain is typically warranted, the management of unruptured AVMs remains controversial. Despite numerous retrospective studies, only one randomized controlled trial has been conducted, comparing the role of medical management alone to medical management plus surgical and/or radiosurgical intervention in patients with unruptured AVMs: A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA). To great controversy, ARUBA concluded that medical management alone was superior to intervention for unruptured AVMs, which was subsequently challenged by various single-institution and multi-center studies analyzing outcomes of ARUBA-eligible patients. This review summarizes studies returned from a PubMed database search querying, 'ARUBA,' 'ARUBA-eligible,' 'surgery unruptured AVM,' and "radiosurgery unruptured AVM". The rates of the primary endpoint of symptomatic stroke or death were low among the analyzed studies (0–12.2%, mean 8.0%) and similar to the medically managed arm of ARUBA (10.1%). Likewise, the percentage of patients with impaired functional outcomes (modified Rankin score $\geq$2) in the reviewed studies was low (5.9%–13.1%; mean: 9.9%) and comparable to the 14.0% observed in the medically management arm of ARUBA. The key findings of ARUBA and subsequent work in its aftermath are overviewed and analyzed for the role of surgery and/or radiosurgery in patients with unruptured AVMs.

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1. Introduction

Although intervention is typically indicated for ruptured brain arteriovenous malformations (AVMs), its role in the management of unruptured AVMs remains unclear [1]. The therapeutic options for patients harboring AVMs include surgical resection, stereotactic radiosurgery, embolization, or any combination of the aforementioned modalities. The decision to pursue intervention is based on many patient and AVM characteristics. Various criteria, including patient age, lesion size and location, and prior history of intracerebral hemorrhage are amongst many relevant attributes [2]. The Spetzler-Martin grading system has been shown to be a reliable tool to predict morbidity and mortality following surgical resection of AVMs (Table 1) [3] and was later revised by the introduction of the Lawton-Young supplementary scale, which included patient age, hemorrhagic presentation, nidal diffuseness, and deep perforating artery supply as additional variables to consider in selecting AVM patients for surgery [4]. In general, patients with Spetzler-Martin grade I and II lesions benefit from surgery, with minimal risk of permanent neurological morbidity or death [5–7]. In 2011, a meta-analysis of 13,698 patients from 137 studies concluded that while overall case fatalities were low, there was still a considerable risk of significant complications leading to permanent neurological deficits after AVM resection, radiosurgery, and embolization, ranging from 5.1% to 7.4% of patients [8]. Rates of complete AVM obliteration were significantly greater in patients who underwent resection (96%), compared to those treated with radiosurgery (38%) or embolization (13%). The study concluded that future randomized controlled trials (RCT) comparing different treatment regimens were needed.

2. A Randomized trial of unruptured brain arteriovenous malformations

In 2014, the interim results from A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) were reported, comparing medical management alone to medical management with interventional therapy in adult patients with unruptured AVMs [9]. Over a period of six years, this multicenter study enrolled 223 AVM patients and allocated 109 to medical management (i.e. pharmacologic treatment of neurological symptoms, as needed) and 114 to intervention including surgery, radiosurgery, and/or embolization. Patients were enrolled into the trial if there was equipoise regarding the benefit of intervention. As such, very few patients received only surgical intervention as few low risk patients with small, non-eloquent AVMs were enrolled in the trial. Notably, the study was halted early due to slow enrollment and because the medical management group exceeded the prespecified stopping point. The rates of the primary outcome (i.e. symptomatic stroke or death) in the as-randomized- analysis were significantly lower in the medical management group compared to the interventional therapy group (10.1% versus 30.7%, respectively; hazard ratio = 0.27). This result was even more pronounced in the as-treated analysis (n = 125, medical management; n = 98, interventional therapy): 8.0% versus 36.7%, hazard ratio = 0.22). In the as-randomized analysis, there were 6 cases of hemorrhagic stroke and 3 cases of ischemic stroke in the medical management group versus 25 and 9 cases of hemorrhagic and ischemic stroke in the interventional therapy group, respectively (hazard ratio for hemorrhagic stroke = 0.25; hazard ratio for ischemic stroke = 0.35). Again, these differences were even more apparent in the as-treated analysis (hazard ratio for hemorrhagic stroke = 0.23; hazard ratio for ischemic stroke = 0.07). There was a significantly higher incidence of focal neurological deficits in the interventional group (14 events, including 4 cases of persistent deficit versus 1 case of a persistent deficit in the interventional therapy and medical management groups, respectively; $p < 0.0001$, as-randomized analysis). Three patients died in the interventional therapy group, including two cases related to the AVM, versus two deaths in the medical management group, neither of which were AVM-related.

The ARUBA study concluded that in unruptured AVMs with interim follow up, medical management alone was superior to medical management with interventional therapy. Subsequently, the results from the ARUBA trial have been criticized on various points, [10–12], the most notable of which include (1) a lack of standardization of the treatment arm in which very few patients with surgically amenable lesions (i.e. Spetzler-Martin grade I and II) underwent resection, (2) short follow-up duration (mean 33.3 months), (3) an excessively high hemorrhage rate in the intervention group (24.5% as-treated), and (4) a lack of data regarding AVM obliteration rates in the intervention group, (5) and a lack of treatment completion in the intervention group, in which more than half of patients had either not completed or initiated therapy at the time of data analysis [5]. Nevertheless, the prospective, randomized design of ARUBA was unprecedented, and it remains the highest level of available evidence regarding the management of unruptured AVMs patients.

Table 1
The Spetzler-Martin grading system is a reliable tool to predict surgical morbidity and mortality.

Spetzler-Martin Grading Scale for AVMs Characteristic	Number of points assigned
Size of AVM	
Small (<3 cm)	1 point
Medium (3–6 cm)	2 points
Large (> 6 cm)	3 points
Location[a]	
Non-eloquent site	0 points
Eloquent site	1 point
Pattern of Venous Drainage	
Superficial only	0 points
Deep component	1 point

[a]Sensorimotor, language, visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, or cerebellar nuclei.

3. Methods

The PubMed database was queried using search terms, 'ARUBA,' 'ARUBA-eligible,' 'surgery unruptured AVM,' and "radiosurgery unruptured AVM,' for publication dates between February 2014 (i.e. the date of ARUBA publication) to August 2016. Case reports and case series (n < 10 patients) were not included.

4. Results

The studies analyzing surgical and radiosurgical outcomes in ARUBA-eligible patients are shown in Table 2. The main outcome measures of interest were the rates of symptomatic stroke or death, which was the primary endpoint in the ARUBA trial, as well as the rates of impaired functional outcomes, defined in ARUBA as a modi-