Medical vs invasive therapy in AVM-related epilepsy

Systematic review and meta-analysis

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ABSTRACT

Objective: To compare invasive arteriovenous malformation (AVM) therapy to conservative management using only antiepileptic drugs (AEDs) for achieving seizure freedom in patients with AVM-related epilepsy.

Methods: We searched Medline, Embase, and Cochrane Central up to June 2015 using epilepsy and AVM Medical Subject Headings and keywords. We included original research involving controlled observational cohort studies or randomized controlled trials (RCTs) comparing seizure outcomes between invasive AVM treatments vs AED management alone, and uncontrolled case series of invasive AVM therapy for seizures that contained ≥ 20 patients. The estimates of seizure freedom were pooled using meta-analysis for the controlled trials, while the estimates for the case series were evaluated using descriptive statistics.

Results: Of 2,166 identified abstracts, 98 were reviewed in full text, of which 31 were included in the final dataset. We identified 2 controlled observational studies ($n = 106$ patients) and 29 uncontrolled case series. We identified 1 RCT but it did not report seizure outcomes. The pooled risk ratio for seizure freedom in controlled studies (0.99; 95% confidence interval [CI] 0.69, 1.43) did not indicate superiority to either approach. Seizure freedom in case series varied from 19% (95% CI 11, 30%) to 95% (95% CI 76, 99%) at last follow-up.

Conclusions: There is insufficient evidence available to determine if invasive AVM management is superior to AED only for controlling seizures. An RCT of interventional vs medical management using standardized epilepsy-specific presurgical protocols is warranted. *Neurology*® 2016;86:64–71

GLOSSARY

AED = antiepileptic drug; **ARUBA** = A Randomised Trial of Unruptured Brain Arteriovenous Malformations; **AVM** = arteriovenous malformation; **CI** = confidence interval; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **RCT** = randomized controlled trial; **RR** = risk ratio.

The annual risk of intracerebral hemorrhage (ICH) from a previously unruptured arteriovenous malformation (AVM) may be as low as 1%.¹ Invasive therapy (neurosurgery, embolization, or stereotactic radiosurgery) for these patients remains controversial. A Randomised Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) has suggested that routine invasive therapy designed to reduce the future risk of ICH may be harmful in patients with unruptured AVMs.¹

Targeted intervention for those with AVM-related epilepsy may be effective, however. Up to one-quarter of people with an AVM initially present to medical attention because of a seizure.² The subsequent 5-year risk of developing epilepsy after a first-ever seizure in patients with AVMs is 58% (95% confidence interval [95% CI] 40%–76%).² Invasive therapy could be useful since early intervention may yield better seizure outcomes.³ Additionally, there may be a higher incidence of hemorrhage in patients with AVM-related epilepsy.³

Current management of AVM-related epilepsy includes antiepileptic drugs (AEDs), resective surgery, endovascular embolization, and stereotactic radiosurgery. The ARUBA trial emphasizes the fact that the overall benefit of invasive AVM treatment in those with AVM-related epilepsy

Supplemental data
at Neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

must be demonstrated to outweigh the risks before these procedures can be universally accepted as routine practice. Therefore, the objective of this study was to compare seizure outcome in patients with AVM-related epilepsy who undergo conservative medical (AED-only) therapy vs invasive AVM therapy for the management of AVM-related epilepsy.

METHOD Search strategy. This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines in June 2015. Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol that was not published. Medline (from 1946 to June 2015), Embase (from 1947 to June 2015), and Cochrane Central were searched using a comprehensive strategy supported by an information specialist and validated search terms from a Cochrane Review of intracranial vascular malformations.⁴ The search incorporated Medical Subject Heading and text words for AVMs, epilepsy, and invasive procedures (appendix e-1 on the *Neurology*[®] Web site at Neurology.org). The references of included articles were hand-searched and experts in the field were consulted to ensure that unpublished data or pertinent studies were not overlooked.

Eligibility criteria. Invasive treatment of AVMs was defined as resective surgery, embolization, stereotactic radiosurgery, or a combination of these procedures. We defined medical management of AVMs as treatment restricted only to pharmacologic therapy (i.e., AED seizure management only). Studies were included if they contained original patient data, irrespective of age, date of publication, language, or country of origin. Only randomized controlled trials (RCTs) and controlled observational studies that directly compared medical management alone to invasive treatment for seizure management in those with radiologically definite AVMs and epilepsy were included in the meta-analysis. Although not included in the meta-analysis (due to an excess of statistical heterogeneity), case series of invasive AVM treatment lacking a comparative medical management arm were also reviewed irrespective of language and study location as long as they contained ≥ 20 patients. These were evaluated descriptively. Studies of any type were excluded if seizure freedom was not reported.

Study selection and data collection. One author (C.B.J.) performed the literature search, and 2 authors (C.B.J., K.S.) independently screened study titles and abstracts using the inclusion and exclusion criteria. Abstracts selected by either or both reviewers were included for the full-review stage.

The same 2 authors (C.B.J., K.S.) reviewed full-text articles in duplicate. If multiple articles reported data on the same population, the most comprehensive publication was selected for inclusion. We resolved disagreement through discussion and a senior author (F.C., S.W., N.J.) was included where necessary.

Two authors (C.B.J., K.S.) independently extracted data in duplicate from the included articles using a standardized data abstraction form. Disagreement was resolved through consensus discussion with a senior author where necessary (N.J.).

The data extracted included year of publication, the country in which the study was conducted, the study design, and the number of participants. Demographic data, stratified by intervention vs medical management, included sex distribution, mean or median age at study inception or intervention, history of intracerebral

hemorrhage or cerebral infarction, and duration of epilepsy. The imaging modalities used to identify AVMs were recorded.

We documented AVM characteristics for both the invasive and medical management groups by recording the distribution of AVM locations (lobar, deep, or infratentorial), mean or median size of the nidus, the distribution of venous drainage patterns (superficial, deep, or both), mean or median Spetzler-Martin grade,⁵ and the proportions of AVMs with associated aneurysms.

The methods of case ascertainment and the types of interventional procedures (surgery, radiosurgery, embolization, or multidisciplinary combination therapy) were documented. We summarized the number of patients undergoing each type of procedure, and, where possible, the purpose of the procedure (whether the intent was to obliterate the AVM or simply to reduce its size) along with the mean or median number of procedures required per patient, and whether a presurgical epilepsy workup, with or without electrocorticography or invasive mapping, was used prior to any intervention. The number of patients who had imaging-confirmed AVM obliteration on follow-up neuroimaging was recorded. The proportion of patients with epilepsy experiencing adverse events in each group was also documented.

The duration of follow-up for each group was also recorded, along with the number on AEDs at the end of follow-up. Seizure outcome was stratified by Engel class⁶ (Class I: seizure-free or only auras since surgery; Class II: rare seizures defined as ≤ 2 per year or only nondisabling nocturnal seizures; Class III: reduction of seizure frequency $\geq 75\%$; Class IV: unchanged or $< 75\%$ reduction of seizure frequency) at last follow-up from the point of initiation of medical management in the conservative arm and the point of intervention in the invasive arm.

Quality evaluation and data extraction. We used the 8-item Newcastle-Ottawa Scale to examine the quality of cohort studies.⁷ While this scale provides an overall score (where a higher score equates to higher quality), the individual items were also compared.

Statistical analysis. The statistical analysis plan was determined in advance of the study. We used parametric descriptive statistics when the data met a normal distribution and nonparametric statistics when they did not. We made the a priori decision to dichotomize seizure outcomes (Engel Class I [free of disabling seizures] vs Engel Class II–IV) at last patient follow-up. Study-specific risk ratios (RRs) were calculated for controlled observational studies and RCTs (if available). The Mantel-Haenszel random effects model was used to obtain a pooled RR. The a priori decision to use a random effects meta-analysis was based on the hypothesis that there was potential for considerable heterogeneity due to variation in study design. Between-study statistical heterogeneity was assessed using the Cochran Q test and the I^2 statistic, and publication bias was explored using visual inspection of a funnel plot. Meta-analyses were conducted using RevMan5.2.3⁸ and Stata version 13.0.⁹

RESULTS Study selection and data collection. Our search identified 2,166 unique articles (figure 1). A total of 98 studies were selected for full-text review, of which 31 were included in the final dataset. No RCTs were identified that reported seizure outcomes. Two controlled observational cohort studies met all eligibility criteria ($\kappa = 0.977$), while 29 uncontrolled cases series were identified. The most common reason for study exclusion was the absence of seizure outcome

Figure 1 PRISMA flow diagram

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. Search conducted on June 26, 2015.

data ($n = 30$; figure 1). Additional studies were not identified after hand-searching references and contacting experts.

Controlled observational cohort study characteristics.

Two controlled observational studies comparing seizure freedom between those undergoing interventional treatment and those undergoing conservative medical management for AVMs were included in the meta-analysis of seizure outcome.^{10,11} Both studies had similar sample sizes, population demographics, and AVM characteristics (table 1). Similar rates of invasive treatment-related AVM obliteration were obtained in each study (75%¹¹ vs 72%¹⁰). The follow-up periods ranged from 4.6 years to 13 years. There was a substantial gap in the time of data collection between the 2 studies; one¹¹ was a retrospective review of tertiary care cases from 1966 to 1979, while the second¹⁰ was a prospective, population-based study reporting on data from 1999 to 2011.

Study quality. The differences in study quality were related to representativeness of the exposed cohort, comparability of the cohorts, and evaluation of seizure freedom (table 2). The more recent publication¹⁰ was given a higher quality rating in each of these areas because the data were population-based (rather than derived from a single center); the authors reported potential confounding variables such as age,

sex, and size of AVM; and the assessment of the seizure freedom was clearly outlined and explained. None of these above factors was addressed in the earlier study.¹¹ The interventional and medical management arms were otherwise comparable apart from the invasive group being slightly younger in one study.¹⁰

Meta-analysis of seizure freedom. The 2 controlled studies comprised a total of 106 patients (interventional treatment $n = 47$; conservative medical management $n = 59$). The studies found no statistically significant difference in the proportion of patients who were seizure-free following invasive AVM therapy compared to medical management. The point estimate of the earlier study from the United States¹¹ favored surgical management while that for the Scottish study¹⁰ favored medical management. No evidence of statistical heterogeneity was found between the 2 studies, using both the I^2 statistic ($I^2 = 0\%$) and Cochran Q statistic ($p = 0.96$). The pooled relative risk of seizure freedom at last available follow-up between AED-only management and invasive AVM therapy was 0.99 (95% CI 0.69, 1.43; figure 2).

Publication bias. It was not possible to perform an Egger small sample test for publication bias due to the limited number of studies. However, the overall pooled estimate did not favor surgical management,

Table 1 Study-level characteristics of studies included in the meta-analysis

Study country	Year of data collection	Study design, case selection	Population characteristics	AVM characteristics	Intervention used	Follow-up period, y	Seizure outcome, method of outcome evaluation
USA ¹¹	1966–1984	Retrospective cohort, hospital	Conservative (n): 26; intervention (n): 20; age: overall epilepsy (mean) 23 y; sex: overall 46% female; AED at last follow-up: conservative 100%; intervention not reported	AVM location: 100% supratentorial; AVM size: not reported; obliteration: intervention (subsample) 75%	Surgical resection	Conservative 13; intervention 4.6	Seizure freedom, chart review
Scotland ¹⁰	1999–2011	Prospective cohort, population	Conservative (n): 21; intervention (n): 39; age: conservative (median) 49 y; intervention (median) 37 y; sex: conservative 28.6% female; intervention 38.5% female; AED at last follow-up: conservative 76%; intervention 74%	AVM location: conservative 100% lobar; intervention 92% lobar; AVM size: median 3.0 mm; obliteration: conservative 5%; intervention 72%	Surgical resection, embolization, radiotherapy	5	Seizure freedom, chart review and patient questionnaire and GP questionnaire

Abbreviations: AED = antiepileptic drug; AVM = arteriovenous malformation; GP = general practitioner.

a finding that mitigates some concerns for publication bias.

Uncontrolled case series of invasive AVM therapy. We identified 29 uncontrolled case series of invasive AVM treatment for seizures that comprised ≥ 20 patients. Study-level characteristics are reported in table e-1.^{12–40} Three studies reported outcomes stratified by type of invasive therapy. Therefore, there were 4 studies evaluating AVM embolization, 17 evaluating radiosurgery, and 12 evaluating surgery; these were evaluated both as a composite whole (29 studies; figure 3A) and individually by modality by extracting data specific to each invasive technique in studies evaluating multiple approaches (figure 3B). Only one surgical series reported using preoperative video-EEG monitoring (15/86 patients; 17%).¹⁹ All studies reported length of the follow-up periods, which ranged from 2 to 20 years (median 8.25 years). There was significant heterogeneity ($P = 94.5\%$; $p < 0.001$) when all modalities were assessed as a composite whole (figure 3A). The median complete seizure freedom at last follow-up

was 59% (interquartile range [IQR] 47%–75%; figure 3A). There was also significant statistical heterogeneity between studies when stratified by modality ($P = 92.5\%$, $p < 0.001$ for embolization; $P = 93.4\%$, $p < 0.001$ for radiosurgery; $P = 89.5\%$, $p < 0.001$ for surgery). Median seizure freedom stratified by AVM intervention type was 54% (IQR 29%–73%) for embolization, 52% (IQR 37%–66%) for stereotactic radiosurgery, and 73% (IQR 56%–79%) for resective surgery (figure 3B). These outcomes were relatively comparable to the proportion of patients who obtained seizure freedom in the 2 identified controlled studies (57% [95% CI 35, 79%]¹⁰ and 46% [95% CI 26, 65%]¹¹).

DISCUSSION Invasive brain AVM therapy is regularly used for those with drug-resistant AVM-related seizures. Despite this, no RCTs and only 2 controlled observational studies published since 1946 were identified that directly compared invasive brain AVM management to medical management alone (using AEDs) in patients with AVM-related epilepsy.^{10,11} The pooled, weighted RR of 0.99 (95% CI 0.69, 1.43) is equivocal and does not indicate superiority to either approach in achieving seizure freedom. An additional 29 studies reported outcomes of interventional management of AVMs only.

Any decision to proceed with interventional therapy must be carefully reached by balancing the anticipated benefits against all reasonably expected risks. The ARUBA trial¹ highlights the importance of empirically establishing risk–reward relationships prior to performing invasive therapies even if, in theory, they should be beneficial. The ARUBA trial enrolled patients with unruptured AVMs representative of typical cases considered for interventional management. The goal was to reduce the future risk of symptomatic stroke and death but, paradoxically, the hazard of death or symptomatic stroke over

Table 2 Newcastle-Ottawa Scale results for the 2 studies included for meta-analysis

Study item	Reference 10	Reference 11
Representativeness of exposed cohort	1	0
Selection of nonexposed cohort	1	1
Ascertainment of exposure	1	1
Demonstration that outcome of interest was not present at start of study	1	1
Comparability of cohorts on basis of study design	2	0
Assessment of outcome	1	0
Was follow-up long enough for outcome to occur?	1	1
Adequacy of follow-up of cohorts	1	1
Newcastle-Ottawa Scale overall score	9	5

Figure 2 Probability of achieving seizure freedom following invasive AVM therapy vs medical management alone

The results of a random effects meta-analysis displaying the pooled estimate of the risk ratio of medical therapy (antiepileptic drug only) vs invasive arteriovenous malformation (AVM) management for achieving complete seizure freedom in patients with AVM-related epilepsy for all included studies. CI = confidence interval; M-H = Mantel-Haenszel.

33 months of follow-up (hazard ratio 0.27; 95% CI 0.14, 0.54) and risk of disability (defined as a modified Rankin Scale score ≥ 2) was significantly higher in the invasive treatment group (46.2%) compared to the medically managed arm (15.1%).

Targeted invasive management may be useful for specific subpopulations. Those who have experienced prior intracranial hemorrhage may benefit, as may those who have drug-resistant epilepsy. Few controlled studies and no RCTs exist that compare conservative AED management alone to invasive brain therapy in those with AVM-related epilepsy. The 2 studies that exist suggest no difference between the 2 approaches, although the precision of the pooled estimate (95% CI 0.69, 1.43) is limited by the paucity of studies and the low number of participants ($n = 106$).

The case series consisting of ≥ 20 participants with epilepsy likely provide inflated estimates of seizure freedom due to the inherent limitations of this study design. They often provide low-quality evidence due to the high risks of selection bias, reporting bias, confounding, the lack of control arms, methods of follow-up, inconsistent length of follow-up, and the limited external validity due to highly selected patient populations. Despite what are almost certainly overestimates of benefit, the proportions achieving seizure freedom reported in these case series are relatively comparable to that observed in the medical arms of both studies included in this analysis (46% [95% CI 36, 56%]¹¹ and 57% [95% CI 35, 79%]¹⁰).

The role of epilepsy surgery vs vascular surgery remains unaddressed. Only one publication reported the use of presurgical video-EEG monitoring but this was only used in a minority (17%) of its study population.¹⁹ An organized presurgical evaluation using standardized video-EEG and volumetric MRI protocols is infrequently employed for vascular malformation-related epilepsy.⁴¹ Lack of such protocols may result in missed dual pathology that can account for the patient's epilepsy. Furthermore, the epileptogenic process results from aberrant surrounding parenchyma and not

on the lesion itself per se. Hence, simple removal of the AVM may not be adequate to achieve complete seizure freedom.

Rates of adverse events between the interventional and medical arms will form a crucial component of future studies. The risk of permanent neurologic deficit or death occurs in a median of 7.4% (range 0%–40%) after microsurgery, 5.1% (range 0%–21%) after stereotactic radiosurgery, and 6.6% (range 0%–28%) after embolization.⁴² Additional, high-quality comparative effectiveness studies will be crucial to confirm these results, and balance them against seizure freedom and putative reductions in the risk of future ischemic or hemorrhagic stroke.

Our analysis benefited from a comprehensive search strategy without restriction on date, language, or country of origin. Our search strategies incorporated validated terms employed by prior Cochrane Reviews of epilepsy and AVM management. However, our study is not without limitations. The possibility remains that studies may have been missed despite our comprehensive search strategy, but this is unlikely.

The main limitations relate to the dearth of studies and quality of the evidence. All studies fail to adequately describe the seizure course of patients including the percentage resistant to medical management, the duration of epilepsy, and the number of medications tried prior to any intervention. Rather, all patients were analyzed as singular heterogeneous entity irrespective of whether they were drug-resistant or not. No attempts were made to stratify between the postintervention course of drug-sensitive and drug-resistant patients. This is critical since typically only those with drug-resistant seizures would be considered for invasive seizure-specific therapy. The meta-analysis ultimately contained only 2 studies comprising a total of 106 patients. It is therefore not surprising that the point estimate is imprecise with a corresponding 95% CI that covers the entire spectrum from benefit to neutral to harm. The absence of RCTs limits comparability of patients

Figure 3 Proportion seizure-free at last follow-up in all case series and according to intervention

Forest plot of the proportion of patients achieving seizure freedom at last follow-up for all case series containing ≥ 20 patients. Overall estimates are presented as medians (interquartile range [IQR]) for all studies (A) and stratified by arteriovenous malformation intervention type (B). CI = confidence interval.

undergoing each intervention and raises concerns about residual confounding. Differing study design and the limited availability of advanced diagnostic modalities in the 1980s would be expected to lead to between-study heterogeneity. Poor reporting of clinical characteristics, including duration of epilepsy and preoperative workup, and divergent approaches to follow-up methodology are also concerning for between-study variance. Finally, varying durations of follow-up are further expected to contribute to between-study heterogeneity. Future attempts at

meta-analysis will be facilitated by the use of uniform methodology, standardized follow-up duration, and outcome measures that include uniform measures of seizure freedom.

There is currently insufficient evidence available to determine if invasive AVM management is superior to AED treatment only for seizure freedom measured at last follow-up. The ARUBA trial, which did not document rates of seizure freedom, strikes a note of caution for the universal use of invasive interventional AVM management.

Invasive AVM therapy for seizures may outweigh the risks reported in ARUBA if it alters the natural history of epilepsy. Sudden unexpected death in epilepsy is estimated to occur at a rate of 0.9 per 1,000 person-years (95% CI 0.2, 2.7) of appropriately treated patients likely due to drug-resistant seizures.⁴³ Additionally, drug-resistant epilepsy is associated with increased risks of mortality, injury, and significant reductions in quality of life due to stigma and psychiatric comorbidities. If invasive AVM therapy can reduce these attendant risks, then invasive therapy may be favored over conservative management.

A multicenter RCT of interventional vs medical management using standardized epilepsy-specific presurgical protocols is warranted. These patients will need to be properly triaged in a multidisciplinary clinic based on a preponderance of factors that include future risk of hemorrhage, AVM location and Spetzler-Martin grade, and the attendant risks related to uncontrolled seizures. After the results of the ARUBA trial, such an endeavor remains both feasible and opportune.

AUTHOR CONTRIBUTIONS

C.B.J., K.S., F.C., and N.J. all contributed to the design of the study. C.B.J. and K.S. prepared the initial draft of the manuscript and C.B.J., K.S., F.C., S.W., and N.J. all contributed to the revision of the manuscript. C.B.J., K.S., F.C., S.W., and N.J. all agree to the publication of this version of the manuscript.

STUDY FUNDING

C.B.J. is the recipient of the American Brain Foundation/American Epilepsy Society/Epilepsy Foundation/American Academy of Neurology Susan S. Spencer Clinical Research Training Fellowship in Epilepsy and an Alberta Innovates: Health Solutions Clinician Fellowship. K.S. is the recipient of an Alberta Innovates–Health Solutions (AI-HS) graduate studentship and the Canadian League Against Epilepsy graduate studentship award. F.C. is supported by a Harkness/Canadian Foundation for Healthcare Improvement Health Care and Policy Practice fellowship. S.W. is the holder of the Hopewell Professorship for Clinical Neurosciences Research at the Hotchkiss Brain Institute, University of Calgary. N.J. is the holder of a Canada Research Chair Tier 2 in Neurological Health Services Research. The funders had no role in the design, data collection, interpretation of data, or decision to publish this study.

DISCLOSURE

C. Josephson, K. Sauro, S. Wiebe, and F. Clement report no disclosures relevant to the manuscript. N. Jette is on the editorial board of *Neurology*[®]. Go to Neurology.org for full disclosures.

Received May 6, 2015. Accepted in final form August 27, 2015.

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