Outcome after conservative management versus treatment of unruptured brain arteriovenous malformations or their associated arterial aneurysms: prospective, population-based cohort study

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OBJECTIVES

To determine whether, for adults with an unruptured brain arteriovenous fistula or malformation (AVM), there is any difference in long-term outcome between ‘treatment’ (with endovascular embolisation, neurosurgical excision, or stereotactic radiotherapy, used alone or in combination) of the AVM or its associated arterial aneurysm versus ‘conservative management’ (i.e. no treatment of the AVM or associated arterial aneurysm)

1. PARTICIPANTS

1.1. Inclusion criteria

1.1.1. First-in-a-lifetime definite brain AVM diagnosis in 1999-2003 or 2006-2010 inclusive
1.1.2. Definite diagnosis on imaging or pathological examination
1.1.3. Resident in Scotland at the time of first diagnosis
1.1.4. At least 16 years of age at the time of first diagnosis
1.1.5. ‘Unruptured’ AVM at clinical presentation (i.e. AVM was detected incidentally or following epileptic seizure(s), non-haemorrhagic focal neurological deficit, or other symptoms such as headache)

1.2. Exclusion criteria

1.2.1. First diagnosed with an incidental unruptured AVM at autopsy
1.2.2. History of symptomatic spontaneous intracranial haemorrhage (ICH), which was anatomically consistent with AVM location, before the clinical presentation which led to AVM diagnosis

1.3. Baseline covariates

1.3.1. Age at clinical presentation
1.3.2. Sex
1.3.3. Clinical presentation type
1.3.4. Oxford Handicap Scale score at clinical presentation
1.3.5. Intra-arterial digital subtraction angiogram (IADSA) done
1.3.6. AVM Spetzler-Martin grade
1.3.7. Maximum AVM nidus size
1.3.8. AVM nidus location (deep = any location that involves the basal ganglia, internal capsule, thalamus, hypothalamus, limbic system, or corpus callosum; lobar; brainstem; cerebellar)
1.3.9. AVM nidus location ‘eloquence’
1.3.10. AVM venous drainage pattern
1.3.11. Associated arterial aneurysm presence, number and location

*If, following clinical presentation with an unruptured AVM, a subsequent non-ICH clinical event occurred during conservative management and led to AVM treatment, age and the mode of clinical presentation were re-coded to correspond to this subsequent event in the treatment group (although if this was an ICH from an unruptured AVM, we did not do this and simply regarded the ICH as an outcome in the conservatively managed group).
2. **DESCRIPTION OF INTERVENTION**

2.1. Time to first treatment of an unruptured\(^{†}\) AVM or associated arterial aneurysm after clinical presentation

2.2. Type(s) and combinations of treatments
   2.2.1. Aneurysm coiling/clipping
   2.2.2. AVM surgery
   2.2.3. AVM stereotactic radiotherapy
   2.2.4. AVM endovascular embolisation

2.3. Success of AVM obliteration
   2.3.1. Complete obliteration on follow-up imaging (describing modality showing this)
   2.3.2. Partial obliteration
   2.3.3. No follow-up imaging

2.4. Success of aneurysm obliteration
   2.4.1. Complete obliteration (describing modality showing this)
   2.4.2. No follow-up imaging

3. **DESCRIPTION OF COMPARATOR**

3.1. Conservative management
   3.1.1. Co-interventions (e.g. haematoma evacuation) not counted as AVM treatment if they did not treat the AVM or associated aneurysm
   3.1.2. Attempted (but not conducted) AVM treatment
   3.1.3. See also the supplementary analyses, below

4. **OUTCOMES**

4.1. Primary
   4.1.1. Time to the composite outcome of either of the following events:
      4.1.1.1. Death of any cause
      4.1.1.2. Sustained dependence (first occurrence of a participant reaching an Oxford Handicap Scale of 2-5, which was sustained for two successive completed annual postal questionnaires rated by the participant’s general practitioner)

4.2. Secondary
   4.2.1. Time to the composite outcome of any of the following events due to the AVM, an associated arterial aneurysm, or their treatment:
      4.2.1.1. Death
      4.2.1.2. Non-fatal symptomatic ICH
      4.2.1.3. Non-fatal symptomatic cerebral infarction
      4.2.1.4. Non-fatal symptomatic progressive or persistent non-haemorrhagic FND

\(^{†}\) If, following clinical presentation, an ICH occurred from an unruptured AVM before treatment, we did not include these patients in the treatment group and simply regarded the ICH as an outcome in the conservatively managed group.
5. **STATISTICAL ANALYSIS**

5.1. **Comparison groups**
   5.1.1. For all analyses the intervention (treatment of the AVM or associated arterial aneurysm) was compared to the comparator (conservative management).

5.2. **Baseline characteristics**
   5.2.1. We used parametric statistics for between-group comparisons when continuous data obeyed a normal distribution, and non-parametric statistics when they did not. We used odds ratios (OR) and their 95% confidence interval (CI) for categorical variables. We used exact tests when cell counts were <5.

5.3. **Follow-up**

5.3.1. **Inception point**
   5.3.1.1. Conservative management – date of clinical presentation (i.e. symptom onset or medical consultation [if asymptomatic]) that led to an investigation that first diagnosed an AVM
   5.3.1.2. Treatment – date of first treatment of an unruptured AVM or its associated arterial aneurysm
   5.3.1.3. See also the sensitivity analyses, below

5.3.2. **Follow-up**
   5.3.2.1. Uninterrupted annual surveillance of general (family) practitioner and hospital medical records, as well as annual postal questionnaires to general practitioners and consenting participants on each anniversary of AVM diagnosis
   5.3.2.2. Follow-up accrued until 27 May 2013 (at least two years of prospective follow-up from presentation for all)
   5.3.2.3. Completeness of all follow-up evaluated from clinical presentation date until either death of any cause or last available follow-up
   5.3.2.3.1. We quantified completeness of the actual follow-up data we had accrued as a proportion of all the potential follow-up that could have been obtained prior to death or the end of follow-up\(^1\)

5.3.3. **Censoring at the earliest occurrence of**
   5.3.3.1. **Primary outcome**
       5.3.3.1.1. Conservative management group
           5.3.3.1.1.1. first treatment of an AVM or associated arterial aneurysm (apart from for patients with an ICH between presentation and treatment, for whom all subsequent ratings of functional outcome were included, and censoring occurred at last available follow-up)
       5.3.3.1.1.2. last available follow-up
       5.3.3.1.2. Treatment group

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5.3.3.1.2.1. Last available follow-up

5.3.3.2. Secondary outcome

5.3.3.2.1. Conservative management group

5.3.3.2.1.1. first treatment of an AVM or associated arterial aneurysm
5.3.3.2.1.2. last available follow-up
5.3.3.2.1.3. death possibly or definitely not attributable to AVM or associated arterial aneurysm

5.3.3.2.2. Treatment group

5.3.3.2.2.1. last available follow-up
5.3.3.2.2.2. death possibly or definitely not attributable to AVM or associated arterial aneurysm

5.3.4. Analysis method

5.3.4.1. Univariate comparisons: life tables and Kaplan-Meier survival estimates
5.3.4.2. Multivariable comparisons: Cox regression if proportional hazards assumptions are satisfied. Covariates pre-specified for multivariable analyses on the basis of their likely imbalance at baseline, prognostic significance, and data completeness, in hierarchical order for inclusion (not exceeding a 1:10 ratio of covariates:outcomes)

5.3.4.2.1. Age at start of follow-up
5.3.4.2.2. Mode of clinical presentation
5.3.4.2.3. Baseline OHS score (for primary outcome only)
5.3.4.2.4. Deep AVM nidus location (any location that involves the basal ganglia, internal capsule, thalamus, hypothalamus, limbic system, or corpus callosum)
5.3.4.2.5. Deep venous drainage
5.3.4.2.6. Maximum AVM nidus size

5.3.5. Null hypothesis

5.3.5.1. There is no difference between treatment and conservative management.
5.3.5.2. The null hypothesis will be tested against the alternative hypothesis that there is a difference using the log-rank test, with a two-sided alpha value of 0.05.
5.3.5.3. The magnitude and precision of any difference that is detected will be quantified using the adjusted hazard ratio and its 95% CI.

5.3.6. Sample size calculation

5.3.6.1. We did not pre-specify our desired sample size, but instead we sought to identify every new definite unruptured AVM diagnosis over 10 years in one country (mid-2010 population estimate of adults aged ≥16 years = 4.31 million) and to accumulate sufficient numbers of primary and secondary outcomes to enable us to analyse our potential predictors in multivariable analyses.
6. SENSITIVITY ANALYSES

6.1. Primary outcome
   6.1.1. Removal of patients who had an ICH between clinical presentation and treatment from the conservatively managed group

6.2. Secondary outcome
   6.2.1. Inclusion of the period from presentation to first treatment for patients without events in this interval in:
      6.2.1.1. either the conservative management group (violating the requirement for independence between conservative management and treatment groups)
      6.2.1.2. or the treatment group (at the risk of introducing immortal time bias)
   6.2.2. We added events that were possibly due to the AVM, associated arterial aneurysm, or a procedure complication (When assessing outcome events, we also classified whether they were definitely, possibly, or definitely not attributable to the AVM, associated arterial aneurysm, or a procedure complication)

7. SUPPLEMENTARY ANALYSES

7.1. The primary outcome in ARUBA, which is, “the composite event of death from any cause or stroke (haemorrhage or infarction confirmed by imaging)”
   7.1.1. This involved a re-analysis of our secondary outcome:
      7.1.1.1. to also include deaths, non-fatal ICH and non-fatal cerebral infarction that were definitely not attributable to the AVM, associated arterial aneurysm, or a procedure complication
      7.1.1.2. to exclude non-fatal progressive or persistent non-haemorrhagic FND
   7.2. An “intention-to-treat” analysis equivalent to our observational “as treated” analyses, where patients who had treatment attempted (but not ultimately given) were re-allocated to the treatment group.