Delayed Hemorrhage After Treatment of Brain Arteriovenous Malformations (AVMs)

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■ OBJECTIVE: **The risk of delayed hemorrhage occurring greater than 2 years after treatment in brain arteriovenous malformations (AVMs) rarely is reported. In this study, we compare the risk of delayed hemorrhage across different treatment modalities.**

■ METHODS: **We performed a retrospective chart review of treated patients with a single intracranial AVM seen at our institution from 1990 to 2013. Delayed hemorrhage was defined as hemorrhage occurring at least 2 years after last treatment. Survival analysis was used to assess risk of delayed hemorrhage by treatment modalities.**

■ RESULTS: **Our study included 420 patients. Spetzler-Martin grades were as follows: I (12.6%), II (36.2%), III (32.6%), IV (15.0%), and V (3.6%). Average follow-up time is 5.1 years. Twenty-two patients (5.2%) were found to have 28 delayed hemorrhages. Average interval between last treatment and delayed hemorrhage was 7.6 years, with the longest being 24.2 years. Proportions of delayed hemorrhages by treatment modalities were as follows: surgery ± embolization (group I, 9.1%), radiosurgery ± embolization (group II, 63.6%), embolization only (group III, 22.7%), and surgery + radiosurgery ± embolization (group IV, 4.5%). Annualized hemorrhage risk after 2 years for each treatment group was as follows: group I (0.4%), group II (1.2%), group III (3.7%), and group IV (1.7%). Survival analysis demonstrated lowest risk of delayed hemorrhage for group 1 ($P < 0.01$).**

■ CONCLUSIONS: **This study is the first to compare the risk of delayed hemorrhage across different treatment modalities. Surgical resection is associated with the lowest risk for delayed hemorrhage compared with other treatment modalities. Patients with partially embolized AVMs should seek timely definitive treatment to decrease the risk of delayed hemorrhage.**

INTRODUCTION

Intracranial hemorrhage (ICH) is the most common complication of brain arteriovenous malformation (AVM) and is associated with significant morbidity and mortality.[1-5] Previous studies on the natural history of AVMs reported significant risk of hemorrhage in patients with this diagnosis. There is a 30%–82% risk of hemorrhage upon presentation[3,6-8] and a subsequent 1.9%–4.61% annual risk of hemorrhage if left untreated.[1,4,9-13] The risk is further increased in AVMs of smaller size, intranidal aneurysms, deep venous drainage, and infratentorial location.[6,8,14-16] In addition, those in the nonwhite population were found to have a greater risk of hemorrhagic than the white population.[15,17] Therefore, for patient populations with characteristics suggesting a high risk of hemorrhage,[2,3,9] treatment strategies should aim to completely obliterate the AVM to protect patients from subsequent hemorrhages.[5]

Risk of hemorrhage after treatment differs across treatment modalities. Posttreatment hemorrhages in surgical series are rare occurrences and are considered to be associated with incomplete resection of the AVM.[18] In contrast, the follow-up course of patients treated with stereotactic radiosurgery (SRS) is more complicated and is usually divided into a latency period and a nonlatency period. A large amount of literature focuses on the risk of bleeding within the latency period, which is reported to be 1%–3.6% per year depending on lesion characteristics[19-24];

Key words
- Arteriovenous malformation
- Delayed hemorrhage
- Latency period
- Posttreatment

Abbreviations and Acronyms
AVM: Arteriovenous malformation
DH: Delayed hemorrhage
ICH: Intracranial hemorrhage
NDH: No delayed hemorrhage
SRS: Stereotactic radiosurgery

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In contrast, the risk of hemorrhage beyond this period is rarely reported, and current estimation is approximately 0.3%–1.3% per year.[23,25,26] For patients undergoing embolization as the only treatment modality, the cumulative risk of developing ICH has been reported as 5.3%, 4.9%, and 1.1% for perioperative period, subacute period, and follow-up period, respectively.[27]

Despite the emphasis on posttreatment hemorrhagic risk in the existing literature, the comparative risk of delayed hemorrhage (DH) across different treatment modalities has not been clarified. We aim to accomplish this by comparing the rate of DH in patients receiving different treatment modalities.

METHODS

Patient Population and Data Collection

We retrospectively reviewed all patients diagnosed with a single intracranial AVM and evaluated in our Institution from January 1990 to December 2013. Patient information was retrieved from our institutional review board–approved AVM database. Only treated patients with at least 1 follow-up were included in this study. Patients who were diagnosed with multiple AVMs, hereditary hemorrhagic telangiectasia, and/or extracranial AVMs were excluded from the study. We also excluded patients with missing information needed for this analysis.

A total of 531 patients had a single intracranial AVM and received treatment. Of these patients, 108 (20.3%) were lost to follow-up, and 3 (0.6%) were found to have missing imaging data. Therefore, after application of our inclusion and exclusion criteria, a total of 420 eligible patients (79.1%) were enrolled into the study. A detailed flowchart of our study cohort selection process is depicted in Figure 1.

Baseline Characteristics and Definition of Variables

Patients were divided into 2 groups for baseline comparison: no delayed hemorrhage group (NDH) and DH group. Patient demographic data, clinical data, angiographic data, and follow-up data were retrieved from the database for evaluation and comparison between the 2 groups. Our demographic factors included age at diagnosis, sex, and race. Clinical data included presenting symptoms and hemorrhagic presentation caused by AVM rupture. Angiographic features included AVM size, location, venous drainage pattern, Spetzler-Martin grading, associated aneurysms, and feeding arteries. Associated aneurysms were defined as intranidal aneurysms or feeding artery aneurysms. Treatment modality was defined as type of treatment patient received before the occurrence of DH and was divided into 4 groups: surgery ± embolization (group I), radiosurgery ± embolization (group II), embolization only (group III), and surgery + radiosurgery ± embolization (group IV). Our definition of follow-up period was the interval between first treatment and last follow-up.

Survival Analysis for DH

In concordance with the goal of this study, we defined DH as hemorrhagic events attributable to AVM rupture and occurring at least 2 years after the last treatment. The cutoff was selected on the basis of previous observations of latency period of radiosurgery.[23,28,29] This definition was applied to all treatment modalities to accommodate the latency period for SRS. Kaplan-Meier survival analysis was used to assess the risk of DH for different treatment modalities. For patients with DH, the time-to-event was defined as the interval between last treatment and the first DH; for the rest of the cohort, time-to-event was defined as the follow-up time.

Statistical Analysis

A Wilcoxon rank-sum test was used for continuous variables. The Fisher exact test was used for categorical variables with individual cell sample size <5, and an uncorrected χ^2 test was used for individual cell sample size ≥ 5. Log-rank test and Poisson-rate test were used for Kaplan-Meier survival curve and patient-time analysis respectively. All P values were reported as 2-sided, and all statistical analyses were performed using R Statistical Software (Version 3.1.1, 2013, Vienna, Austria).

RESULTS

Baseline Characteristics

Average age for all patients in this cohort was 35.0 years, and 180 patients (42.9%) were men. Patients in the DH group were significantly younger than patient in the NDH group (26.1 years vs. 35.5 years, $P < 0.01$). No significant difference between the 2 groups was observed for sex ($P = 0.53$) and race ($P = 0.88$). Ruptured presentation occurred in 157 (37.4%) patients, with 146 patients (36.7%) in NDH group and 11 patients (50.0%) in DH group. No significant difference was observed between the 2 groups for all presenting symptoms. A detailed description of all baseline characteristics can be found in Table 1.

Spetzler-Martin grading of the lesions were: I ($n = 53$; 12.6%), II ($n = 152$; 36.2%), III ($n = 137$; 32.6%), IV ($n = 63$; 15.0%), V ($n = 15$; 3.6%). Patients in the DH group generally have larger AVMs (3.8 cm vs. 2.9 cm, $P < 0.01$) and greater Spetzler-Martin grading ($P = 0.04$) compared with the NDH group. We did not find significant differences for other angiographic features between the 2 groups, although there is a trend towards significance for basal ganglia/thalamus location (DH 18.2% vs. NDH 7.0%, $P = 0.08$).

Follow-up time was 5.1 years for all patients, with DH group patients having a significantly longer follow-up time (7.7 years, $P < 0.01$). This can be explained by the fact that patients with DH have greater grades and are more likely to undergo nonsurgical management, which generally requires a longer follow-up time. Our data demonstrated that more patients (22.7% vs. 5.8%, $P < 0.01$) were chosen for group III (embolization only) treatment in the DH group compared with the NDH.

Risk of DH

A total of 22 patients (5.2%) experienced 28 DH events over a total of 2341.153 patient-years, which translates into 12.0 events per 1000 patient-years, or an annualized risk of 1.2% per year after 2 years after treatment. Detailed description of all patients can be found in Table 2 and Figure 2. Kaplan-Meier survival analysis for all treatment groups demonstrated a cumulative survival from DH of 56.0% over at 24.2 years. An overview of the overall survival curve is depicted in Figure 3A.

We further divided the cohort into 4 treatment groups for comparison (Figure 3B). As described in Table 3, group I (surgery ± embolization, $n = 122$) demonstrated superiority (P