Safety of Select Headache Medications in Patients with Cerebral and Spinal Cavernous Malformations

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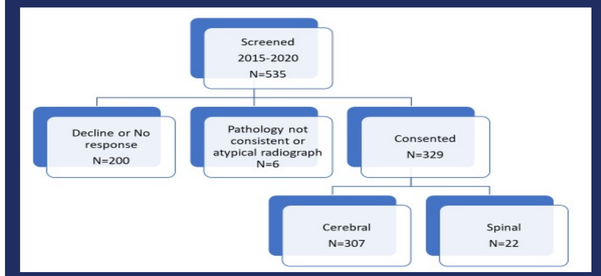
Background

- Cavernous malformations (CM) are vascular malformations of the brain and spinal cord consisting of endothelial lined caverns devoid of smooth muscle.
- Clinical presentations of CM range from asymptomatic lesions discovered incidentally on neuroimaging (MRI) to seizures and hemorrhage.
- Headache has been reported in 4 to 52% of symptomatic patients.
- Given the risk of bleeding associated with CM, and the vascular nature of the lesion, uncertainty about the use of non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs) and triptans have arisen leaving few acute treatment options for headache
- In addition, a case report raised concern that OnabotulinumtoxinA, used for chronic migraine, led to bleeding from a CM in that single patient.
- We aimed to determine the safety of NA-NSAID, triptan and OnabotulinumtoxinA in a large, prospective cohort of patients with cerebral and spinal CM.

Methods

- With IRB approval, we have maintained a prospective data base of patients with radiographic evidence of cerebral or spinal CM seen at our institution beginning in January of 2015. All adult patients with CM of the spinal cord or brain were screened. Those consented to participation were included.
- Patients were excluded if they were under 18 at the time of their visit to our institution, pathology at surgery demonstrated an alternative etiology, or if they had a Zabramski Type 4 lesion.
- Initial and follow up data were obtained by review of electronic medical record in addition to mailed written surveys and in person follow up. Patients received a written survey at the enrollment, then annually for 5 years. We recorded any new symptomatic hemorrhages and verified any reported hemorrhage.
- Univariate logistic regression models were used to assess risk factors for prospective hemorrhage.

Figure 1: Screening and Consenting



Results

- Between 2015 and October 1, 2020, 535 patients were screened; 329 patients consented. (Figure 1 and Table 1)
- The total follow-up time from the time of diagnosis to time of first censor (first prospective hemorrhage, complete excision of a sporadic form CM, or death), was 1799.9 patient years.
- There were 92 prospective symptomatic hemorrhages

Table 1: Baseline Demographics

Characteristic	Number (%) N=329
Age at Diagnosis (years)	30.7 +/-11.4
Female	191 (58.0%)
Familial Form	68 (20.1%)
Mode of Presentation	Incidental: 131 (40.0%) Hemorrhage: 139 (42.2%) Focal neurologic deficit: 22 (6.6%) Seizure without hemorrhage: 36 (10.9%) Other: Hydrocephalus: 1 (0.3%)
Multiple CM	94 (28.6%)
Location of CM	Supratentorial-Cortical: 130 (39.5%) Supratentorial – Subcortical: 66 (20.0%) Brainstem: 90 (27.4%) Cerebellum: 18 (5.5%) Spinal Cord: 22 (6.7%) Other: 3 (0.9%) (2 intraventricular; 1 hypothalamic)
Presence of DVA	115 (39.1%)

	All Patients (n=329)	No Prospective Hemorrhage (n=237)	Prospective Hemorrhage (n=92)	P value	Odds Ratio (95% CI)
Age at presentation (years)	30.7 +/-11.4	32.0+/-11.0	27.4 +/-11.7	0.0008*	0.13 (0.36-0.44)
Female sex	191 (58.0%)	137 (57.8%)	54 (58.7%)	0.88	1.03 (0.64-1.69)
Initial Presentation with CM Hemorrhage	139 (42.2)	75 (31.6%)	64 (69.6%)	<0.0001*	4.9 (2.9-8.3)
Brainstem Location	90 (27.4%)	53 (22.3%)	37 (40.2%)	0.0013*	2.3 (1.4-3.9)
NA-NSAIDS	154 (46.8%)	124 (52.3%)	28 (31.8%)	0.0012*	0.44 (0.26-0.72)
Triptan	29 (8.8%)	24 (10.1%)	5 (5.4%)	0.18	0.51 (0.19-1.4)
Onabotulismtoxin A	18 (5.4%)	18 (7.6%)	0	0.0005*	---
Any beta blocker	38 (11.5%)	32 (13.5%)	6 (6.5%)	0.08	0.44 (0.18-1.10)
Propranolol	11 (3.3%)	9 (3.8%)	2 (2.1%)	0.73	0.56 (0.11-2.65)

Results and Discussion

- From the time of diagnosis to time of censor, 154 (46.8%), 29 (8.8%), and 18 (5.4%) of patients reported using NA-NSAIDS, Triptans, or OnabotulismtoxinA respectively. None of these medications were associated with an increased risk of prospective hemorrhage (Table 2). In fact, NA-NSAIDS was potentially beneficial
- Age at presentation, initial presentation with hemorrhage and brainstem location were associated with increased risk of prospective hemorrhage as is consistent with prior literature
- Limitation of the study includes:
- We did not specifically assess the duration, dose, and frequency of the use of the selected medications, and the time from hemorrhage to the timing of first taking the select medications in those who initially presented with hemorrhage

Conclusions

We found that NA-NSAIDS, Triptans, and OnabotulismtoxinA therapy (doses 200 units or less per session) did not precipitate hemorrhage in patients with CM in this cohort and can be considered in select patients with CM for management of primary headache disorders.

Further data from ongoing registries may help assess ongoing safety of these and newer migraine medications