SHORT COMMUNICATION

Effect of Beta-blockers on Extracranial Arteriovenous Malformations

Sarah CHASTANET1, Annabel MARUANI1, Boris LAURE1, Denis HERBRETEAU2 and Aline JOLY1
1Maxillofacial and Facial Plastic Surgery Department, University of Tours, Trousseau Hospital, CHRU Tours, FR-37000 Tours, 2Department of Dermatology, and 3Radiology and Medical Imaging Department, Center of Reference of Vascular Malformations MAGEC-Tours, Bretonneau Hospital, University of Tours, CHRU Tours, Tours, France. E-mail: sarah.chastanet@gmail.com
Accepted Jan 31, 2022; Epub ahead of print Jan 31, 2022
Acta Derm Venereol 2022; 102: adv00680. DOI: 10.2340/actadv.v102.1412

Extracranial arteriovenous malformations (AVMs) are rare congenital high-flow anomalies caused by abnormal vascular development during embryogenesis. Post-zygotic mutations have been evidenced in several recent cases (1, 2). AVMs most commonly affect the head and neck (47.4%) and the extremities (28.5%). Although present at birth, they are commonly not apparent or asymptomatic until later in life. They may grow because of hormonal changes (puberty, pregnancy), and their natural history can follow 4 stages according to the Schobinger classification: (I) quiescent stage, (II) lesion becomes warmer and larger with a thrill, (III) destruction process, such as ulcers, haemorrhages or bony lytic lesions, (IV) heart failure complication that might be life-threatening, due to intense flow (3, 4). The diagnosis of AVMs is suggested by physical examination and requires, for confirmation, vascular imaging studies, including Doppler ultrasonography, magnetic resonance angiography or arteriography (1, 4).

Current therapeutics for AVMs are limited, and multidisciplinary management remains challenging. When possible, the best curative treatment combines embolization and complete surgical resection. In case of embolization only or partial resection, the rate of growth flares is high (3). Other treatments, such as radiotherapy, thalidomide or mammalian target of rapamycin inhibitors have been tested, without significant positive outcomes (3–7).

Propranolol is a non-selective beta-adrenergic blocker indicated for several conditions, including complicated infantile haemangiomias (8, 9). However, it is not efficient in decreasing other vascular tumours. Properties of propranolol (vasoconstrictor, antiangiogenic and pro-apoptotic effects, along with its inotropic properties leading to a decrease in arterial pressure) could be interesting in AVMs. Only a few data are available in the literature (10, 11). The aim of the current study was to investigate the efficacy and tolerance of systemic beta-blockers in extracranial AVMs.

RESULTS

A total of 12 patients were eligible and 7 were included (5 men; 1 patient was not followed in our centre, 2 refused to participate). The median age was 55 years (range 20–67 years) and the median age of discovery of AVM was 17 years (range 0–56 years). Characteristics of patients and AVMs are shown in Table I. In 4 cases, beta-blockers were the first-line treatment for the AVM. Beta-blockers (propranolol in 5 cases and atenolol in 2 cases) were started because AVM progressed slowly, which did not justify a more invasive treatment, or because other treatments were too risky (Table 1). The initial dosage regimen ranged from 7 to 80 mg per day for propranolol and 25 to 50 mg for atenolol, with a median duration of 25 months (range 14–36 months); treatment was still ongoing in 4 patients.

Regarding overall improvement, treatment with beta-blockers was significantly effective, with a mean ± SD overall improvement in self-assessed efficacy of 39.0/100 ± 34.0. The treatment was considered successful in 5 of 7 cases. Mean ± SD self-assessed effects on pain and reduction in volume of the AVM were 6.4/100 ± 10.2 and 21.4/100 ± 26.5, respectively. Two patients reported a benefit in self-perception of pulsation of the AVM, which was described as an annoying symptom. Pre- and per-treatment imaging was available for 4 patients and showed, in all cases, no difference in volume after beta-blockers.

Five of 7 patients experienced side-effects: bradycardia, Raynaud’s syndrome, tiredness, reduced libido,
sadness and chilliness (Table I). One patient discontinued beta-blockers because of a cough related to treatment.

**DISCUSSION**

This study of 7 patients with extracranial AVMs shows that beta-blockers (propranolol and atenolol) were associated with no reduction in volume of the AVM over a median of 14 months, but also with no progression. However, patients perceived an overall improvement, associated with no reduction in volume of the AVM over a median of 14 months, but also with no progression. All other options are not efficient, are only slightly efficient, or have a high rate of recurrence (3–7). Therefore, beta-blockers could be integrated in the therapeutic strategy for management of AVM because they have an acceptable safety profile. Perspective studies will focus on therapies targeted to molecular results for AVMs, but data on the effectiveness and safety of these drugs are not yet available (13).

**REFERENCES**

1. Uller W, Alomari AI, Richter GT. Arteriovenous malformations. Semin Pediatr Surg 2014; 23: 203–207.
2. Couto JA, Huang AY, Konczyk DJ, Goss JA, Fishman SJ, Mulliken JB, et al. Somatic MAP2K1 mutations are associated with extracranial arteriovenous malformation. Am J Hum Genet 2017; 100: 546–554.
3. Liu AS, Mulliken JB, Zurakowski D, Fishman SJ, Greene AK. Extracranial arteriovenous malformations: natural progression and recurrence after treatment. Plast Reconstr Surg 2010; 125: 1185–1194.
4. Lee A, Patel NA. Systematic review of pediatric mandibular arteriovenous malformations. Int J Pediatr Otorhinolaryngol 2021; 150: 110942.
5. Le Fourn E, Herbreteau D, Papagiannaki C, Lorette G, Baseline D, Mulliken JB, et al. Efficacy and tolerance of sirolimus (rapamycin) for extracranial arteriovenous malformations in the extremities and head and neck: a retrospective study of 32 cases. Eur J Dermatol 2015; 25: 52–56.
6. Buscarini E, Botella LM, Geithoff U, Kjeldsen AD, Mager HJ, Pagella F, et al. Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis 2019; 14: 28.
7. Gabeff R, Boccara O, Soupre V, Lorette G, Bodemer C, Herbreteau D, et al. Efficacy and tolerance of sirolimus (rapamycin) for extracranial arteriovenous malformations in children and adults. Acta Derm Venereol 2019; 99: 1105–1109.
8. Albiñana V, Recio-Poveda L, Zarrabeitia R, Bernabéu C, Botella LM, Propranolol as antiangiogenic candidate for the therapy of hereditary haemorrhagic telangiectasia. Thromb Haemost 2012; 108: 41–53.
9. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015; 372: 735–746.

---

**Table I. Characteristics of patients, arteriovenous malformations (AVMs) and beta-blocker treatment**

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Sex, age, years | Male, 56 | Male, 20 | Male, 55 | Male, 41 | Female, 40 | Male, 56 |
| Localization of AVM | Face/head | Upper limb | Face/head | Lower limb | Upper limb | Face/head |
| Family history of vascular anomalies | No | No | No | No | No | No |
| Age at diagnosis of AVM, years | 0 | 17 | 18 | 40 | 40 | 40 |
| Age at treatment initiation | 55 | 0 | 54 | 0 | 38 | 0 |
| Triggering factor of AVM | Weight gain | Surgery | Surgery | No | No | No |
| Treatments performed before beta-blockers | Embolization, radiotherapy | None | Embolization, surgery | None | None | None |
| Schobinger staging | III | I | II | I | I | I |
| Treatment duration (months) | 24 | 3 | 14 | 25 | 33 | 36 |
| Beta-blocker used | Propranolol | Atenolol | Propranolol | Propranolol | Propranolol | Atenolol |
| Dosage regimen (mg) | 80 | 50 | 80 | 60 | 40 | 7 |
| Treatment initiation criteria | Progression of AVM | Bleeding, pain and difficult embolization | Progression and refusal of embolization | Raynaud’s syndrome | None | Cough, tiredness, sadness |
| Side-effects of treatment | Decreased libido | None | Tiredness, chilliness, decreased libido | Raynaud’s syndrome | None | Yes (side-effects) |
| Treatment withdrawal | No | No | Yes | No | Yes (anxiety of long-term treatment) | No |

---

**Notes:**
- All other AVM treatments were performed after embolization.
- Treatment was started at a median of 14 months.
- This study supports that beta-blockers are effective in reducing the volume of extracranial AVMs, but may be of interest in stabilizing the lesions and decreasing symptoms. The best curative option for AVMs is large surgical excision after embolization, but this can rarely be performed. All other options are not efficient, are only slightly efficient, or have a high rate of recurrence (3–7). Therefore, beta-blockers could be integrated in the therapeutic strategy for management of AVM because they have an acceptable safety profile. Perspective studies will focus on therapies targeted to molecular results for AVMs, but data on the effectiveness and safety of these drugs are not yet available (13).
10. Lu J, Anvari R, Wang J, Huang J, Pei S, Xiang Y, et al. Propranolol as a potentially novel treatment of arteriovenous malformations. JAAD Case Rep 2018; 4: 355–358.
11. Rodríguez-Jiménez P, Uceda M, Ramirez-Bellver JL, Ruiz-Rodríguez R, Sánchez-Carpintero I. Oral propranolol as palliative treatment for a recurrent arteriovenous malformation. Dermatol Ther 2019; 32: e13075.
12. Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. In Vitro Cell Dev Biol Anim 2002; 38: 298–304.
13. Edwards EA, Phelps AS, Cooke D, Frieden IJ, Zapala MA, Fullerton HJ, et al. Monitoring arteriovenous malformation response to genotype-targeted therapy. Pediatrics 2020; 146: e20193206.