Neurosurgical Forum

LETTERS TO THE EDITOR

Propranolol for pediatric intracerebral cavernomas: unanswered questions

TO THE EDITOR: I read the case report by Cavalheiro et al.² with interest (Cavalheiro S, do Amaral Campos HG, Silva da Costa MD: A case of giant fetal intracranial capillary hemangioma cured with propranolol. *J Neurosurg Pediatr* 17:711–716, June 2016). Propranolol has been described as a “magic bullet” in the treatment of intracranial cavernomas.^{1,5} The article gives a good summary of the utility of propranolol for the treatment of intracranial capillary hemangiomas. There are a few other articles that have been previously published that were not included in this article, and I believe that presenting them may be beneficial for a wider audience.

There are a few points that need to be carefully considered in this context.

1. Pathology was confirmed in a few cases that were highlighted in the article, and those were cases in which cavernomas were noted in the intracranial and extracranial location and the case in which the lesion was surgically treated and that yielded a postoperative diagnosis.³ With multiple intracerebral cavernomas, we are guided by the MRI findings and genetic analysis if there is a strong family history.
2. Regarding the pathology of cutaneous and intracerebral adenomas: are they similar? We have to accept the fact and the evidence that propranolol works effectively in both cases.
3. Instances in which propranolol cannot stop progression of cavernomas. We published a case report about an infant who had multiple intracranial cavernomas, with a family history of cavernoma noted on the paternal side.⁸ The child underwent multiple surgeries due to symptomatic hemorrhage in the hemispheres and also in the brainstem. The lesions continued to progress and propranolol was started when the child was 8 months old, at a dose of 2 mg/kg/day for 2–3 months. The child unfortunately died due to recurrent hemorrhage and brainstem compromise, despite the administration of propranolol. This was confirmed by an MRI sequence of the brain obtained after 3 months of treatment, when this child was admitted in a critical state.

This raises the potential question of propranolol's utility and benefit in multiple cavernomatoses and familial cavernomatosis. One cannot be guided by a single case experience.

4. Should propranolol be used in asymptomatic children with multiple intracranial cavernomas because it is a reasonably safe drug? Obviously there is enough evidence to suggest how to treat an asymptomatic child with intracerebral cavernoma or cavernomatosis. Can we extrapolate this to familial cavernomatosis? These are the questions that are still unanswered.
5. The acceptable maximal dose for children, and if this can be applied to a wider paediatric group.
6. Utility of propranolol in spinal cavernomas.⁴
7. Can this be applied to the adolescent and adult populations? There are 2 case reports published recently favoring this.^{6,7}

At this juncture we should not underestimate the role of surgery in patients, particularly in those with recurrent hemorrhages and uncontrollable seizures who are taking multiple antiepileptic medications as treatment for intracerebral cavernoma or cavernomatosis. Multidisciplinary management of these patients with input from neurologists, neurosurgeons, and pediatricians is a *sine qua non* and is indispensable.

There is a need for a multicenter, prospective study that may potentially give more answers for these cohorts of patients and may change the way this rare condition is treated by avoiding surgical intervention. We may certainly be in a position to get an answer to two of the above questions—one is the disappearance of the intracranial cavernomas and potential control of seizures with this magic bullet.

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Response

We thank Dr. Kaliaperumal for the issues raised regarding the use of propranolol to treat pediatric intracerebral cavernomas, and the opportunity to progress in the discussion by writing this letter.

The rationale for using propranolol in infantile capillary hemangiomas was developed by Leaute-Labreze et al.³ in 2008. According to their report, propranolol was used in 2 children with infantile hemangioma during corticosteroid treatment, because of cardiomyopathy. However, with the introduction of propranolol, there was a pronounced reduction of the hemangioma, and the observation of this phenomenon led the authors to treat 9 other children, who then also demonstrated success with regard to the regression of their hemangiomas. Since then, many studies have been conducted demonstrating the efficacy of propranolol as a treatment in patients with infantile hemangioma, making it the first-line medication, mainly when the infantile hemangioma is causing a functional or disfiguring aesthetic injury.^{4,5,7}

Within this context, the first fact to be observed is that our publication, in which we have shown a successful treatment of a giant intracranial hemangioma with propranolol, as well as that of Leaute-Labreze et al.,³ refer to infantile capillary hemangiomas or infantile hemangiomas that are considered vascular tumors. The term infantile capillary hemangioma is often confused with cavernous hemangiomas or cavernomas; however, the 2 lesions have different characteristics. In its most recent version (2014), the International Society for the Study of Vascular Anomalies classifies infantile hemangiomas as belonging to the group of vascular tumors because of their neoplastic and, therefore, proliferative characteristics. They are histologically characterized by pericytes and proliferative endothelial cells, and present with the following immunohistochemical markers: glucose transporter 1 (Glut-1), Lewis Y antigen, FCγ II receptor (FcγRII), and merosin.^{6,11} On the contrary, cerebral cavernomas are part of the group of venous malformations, which represent an error in vascular morphogenesis, and are histologically characterized by solitary or multiple nodular aggregates of thin-walled, round, closely packed veins.^{6,11}

Moreover, it is known that cerebral cavernomas present important clinical, radiological, and histopathological dif-

ferences as compared with orbital and skin cavernomas. Orbital cavernomas present a well-defined capsule in surgery and imaging, whereas cerebral cavernomas do not, and are surrounded by a pseudocapsule of hemosiderin. Orbital cavernomas rarely bleed, whereas cerebral cavernomas present with growth by confluent intralesional microhemorrhages that result in 3 clinical signs: hemorrhage, seizures, and tumorlike growth.² We treated 2 children with intraorbital cavernomas who had proptosis, whose lesions disappeared completely. Hejazi et al.² reported evident histopathological differences between intraorbital and cerebral cavernomas, in which the orbital aspects were more similar to those of capillary infantile hemangiomas, whose growth is due to intraluminal thrombosis and subsequent recanalization of the vessels, without signs of hemorrhage.

Propranolol appears to exert vasoconstricting, antiangiogenic, and apoptotic activity in infantile hemangiomas.^{3,8–10} There appears to be a biological plausibility to the use of a drug with these characteristics in a proliferative vascular tumor such as infantile hemangioma, as demonstrated by the excellent clinical response obtained in patients using this medication.^{3–5,7} It remains uncertain whether the action of propranolol can be extrapolated in cerebral or extracranial cavernomas to present the same clinical response as that seen in infantile hemangiomas.

Zabramski et al.¹² and Berti et al.¹ also reported on the use of propranolol in cerebral cavernomas, with good clinical response. The former group reported its use in 2 adult patients and observed regression of the cavernomas and an absence of new bleeding episodes, whereas the latter authors reported on the use of the medication in a child and observed a marked regression of the lesions. However, we also found reports like those of Dr. Kaliaperumal, in which propranolol at a dose of 2 mg/kg/day was used in a severe case of familial cavernoma in a child who did not respond to treatment.

Therefore, because the characteristics of childhood hemangiomas differ from cerebral cavernomas, we doubt whether propranolol treatment would be the best option to consider. On the other hand, some case reports have shown that cerebral cavernoma responds positively to propranolol; hence, it is unclear which patients with cerebral cavernomas will respond to propranolol, how to properly select them, or even if the dose used for treatment should be changed. We know that the dose used for facial infantile hemangiomas is 2 mg/kg/day. We used 3 mg/kg/day for a case with intracranial manifestation. In 2014, the US FDA approved the use of propranolol in solution (Hemangeol; Pierre Fabre Pharmaceuticals, Inc.) for the treatment of infantile hemangiomas at a maximum dose of 3.4 mg/kg/day (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205410orig1s000toc.cfm). Larger doses were not tested for these cases.

We know that propranolol is effective in the treatment of infantile hemangiomas, mainly those with cutaneous involvement, and has demonstrated efficacy in a single case with intracranial injury. We need to carefully analyze its use in patients with cerebral cavernomas. In future, a clinical trial may help us elucidate the efficacy in this group of patients.

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