Topical timolol maleate: An effectual and safe recourse for infantile hemangiomas

Sir,

Infantile hemangiomas (IH) are neoplastic proliferations of endothelial cells affecting approximately 4% of the children in this age group, with prematurity and chorionic villus sampling increasing its incidence.[1] The exact pathogenesis has yet to be elucidated, although they have been postulated to arise from $CD133^+$ stem cells that can differentiate into multiple cell lineages.[2] An imbalance between the expression of angiogenic and antiangiogenic factors has been proposed. Tissue inhibitors of metalloproteinase, an inhibitor of angiogenesis, are expressed in the involution phase while 17-estradiol may play a role in the growth of infantile hemangiomas.[3] Hemangiomas undergo a proliferative phase for 8-12 months followed by subsequent gradual involution over the next 2-10 years.[4] In view of this spontaneous resolution, active intervention is required only for large complicated hemangiomas and active nonintervention should be reserved for uncomplicated hemangiomas. However, due to the cosmetic disfigurement they cause, small uncomplicated hemangiomas in prominent exposed places such as face can be a cause of serious concern to the parents who may demand immediate treatment. A number of treatment modalities have been used over the years including topical, intralesional and systemic steroids, interferons, vincristine, imiquimod, interventional therapies such as cryotherapy, Argon, Nd-YAG, flashlamp-pumped pulse dye laser, embolization, sclerotherapy, surgery, and radiotherapy.

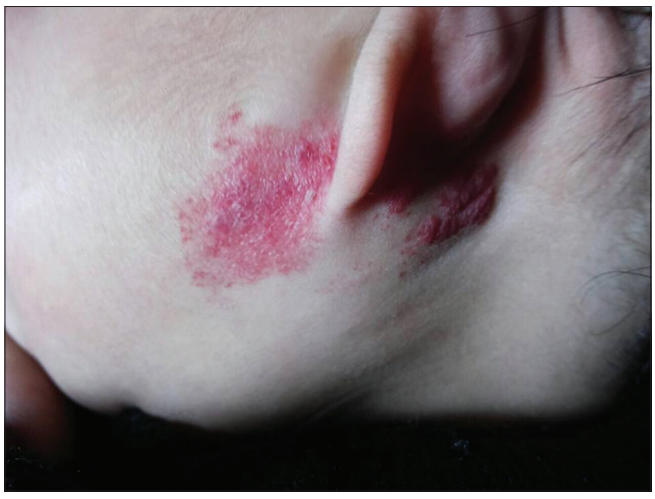

Figure 1: Pretreatment photograph showing infantile hemangioma on the face of the infant

However, due to the many side effects and cost factor associated with these systemic and interventional therapies, safer and topical therapeutic modalities are now being tried in IH, especially uncomplicated, superficial hemangiomas. We herein report a case of IH showing marked response to the topical nonselective β-blocker timolol maleate.

A 9-month-old boy presented with hemangiomas over the left mandibular area, in front of the left ear and also in the ipsilateral retroauricular area. There was no history of ulceration or bleeding from the lesions. However, it had been gradually enlarging since birth causing the parents to seek active treatment despite our reassurance of spontaneous regression. A thorough physical examination was performed followed by routine blood investigations, blood sugar levels, chest radiography, echocardiogram, ultrasound scan of abdomen and magnetic resonance imaging of brain to rule out any associated syndrome such as posterior fossa defects, hemangioma, arterial anomalies, cardiac defects, coarctation of aorta, eye anomalies, sternal clefting, and supraumbilical raphae (PHACES), local ultrasonography of the lesion to determine its depth and measurement of the lesions. Pretreatment photographs were taken [Figure 1] and the treatment was started with twice daily application of 0.5% timolol maleate eye drops, enough to just coat the lesion and to gently rub it in. The first application was done in the outpatient department under supervision, and blood pressure and heart rate were measured just before application and 1 h after application. Repeat blood pressure and heart rate, were taken at weeks 0, 1, 2, 3, 4, 6, and 8. During this period, blood sugar measurement was done weekly. No abnormalities were detected. More than 30% reduction in the hemangioma was observed after 2 weeks of treatment and more than 90% by the end of 2 months as determined by repeat measurements and local ultrasonography of the lesions [Figure 2a and b]. Timolol eye drops were continued with the dosing frequency reduced to once daily. No rebound has been observed during follow up over the last 3 months.

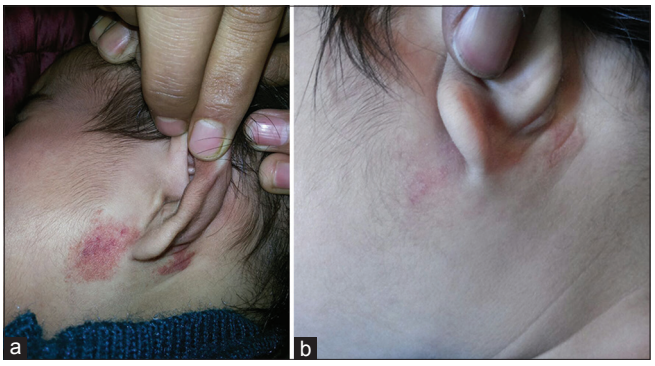

Figure 2: (a) Evolution of infantile hemangioma after application of 0.5% timolol maleate eye drops at 2 weeks. (b) Evolution of infantile hemangioma after application of 0.5% timolol maleate eye drops at the end of 2 months

Timolol maleate is a nonselective β-blocker medication. Although the exact mechanism of action in hemangioma reduction is not clear, it is claimed to reduce the blood flow through hemangiomas by blocking the β-adrenergic receptors thereby making blood vessels tighten. The cells that cause the growth of hemangioma are also affected by timolol so that the hemangioma starts to reduce in size. It inhibits the growth factor responsible for proliferative phase. Later, it aids in apoptosis, which leads to involution of hemangiomas.[5-7] Topical timolol can be used safely in both complicated and uncomplicated hemangiomas with an efficacy similar to the systemic β-blocker, propanolol albeit the onset of action is much earlier (within 48 h) with the latter.[8] Rare side effects reported with the use of topical timolol for pediatric glaucoma include asthma exacerbation and Cheyne stokes breathing.[5] Apart from this, pruritis was reported when used to treat hemangioma with PHACES.[6] Other very rare side effects include bradycardia, hypotension, bronchospasms, peripheral vasoconstriction, fatigue, sleep disturbances, and hypoglycemia. Hence, proper monitoring before and during treatment with topical timolol is required especially when used over large areas. Larger comparative and controlled studies are required in the future to establish topical timolol as an effective treatment modality for IH.

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Conflicts of interest

There are no conflicts of interest.

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