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Successful systemic propranolol treatment for periocular capillary hemangioma in Indonesian infant girls: A case series

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Case Report

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ABSTRACT

Capillary hemangioma (CH) is the most prevalent benign tumour in children. Most cases showed spontaneous involution without any intervention. However, approximately 10% of all CH patients require treatment. Most cases of periocular capillary hemangioma (PCH), especially orbital form, risk significant morbidity; therefore, aggressive treatment is needed. Studies showed a superior outcome of systemic propranolol for CH compared to standard therapy (corticosteroids). We present cases with different PCH types successfully treated with systemic propranolol. Five patients with different types of PCH were given systemic propranolol. One patient presented with a lesion at birth, while others were less than ten months of age. Oral propranolol was given at 0.5 mg/kg body weight (BW) as the initial dose for two weeks. The dose was gradually increased to 2.0 mg/kg BW within 1-18 months of treatment. All patients showed sufficient initial responses regarding mass reduction and colour change within 2-12 weeks. No complications or adverse effects were observed. The regimen of 2.0 mg/kg BW systemic propranolol treatment was considered safe and beneficial for PCH.

Hemangioma kapiler (HK) merupakan tumor jinak tersering pada anak. Sebagian besar kasus menunjukan perbaikan spontan tanpa pemberian intervensi. Tetapi, sekitar 10% kasus HK memerlukan terapi. Sebagian besar kasus hemangioma kapiler periokular (HKP), terutama bentuk orbital, memiliki risiko morbiditas yang signifikan, oleh karena itu diperlukan terapi yang agresif. Studi ini menunjukkan pemberian propranolol sistemik pada HK memberikan hasil terapi yang lebih baik dibandingkan dengan standar terapi terdahulu yaitu kortikosteroid. Studi ini berisi lima laporan kasus dengan tipe HKP berbeda yang berhasil ditatalaksana dengan pemberian propranolol sistemik. Satu pasien datang dengan lesi yang timbul saat lahir, sementara yang lain saat berusia kurang dari sepuluh bulan. Propranolol oral diberikan 0,5 mg/kg berat badan (BB) sebagai dosis awal selama dua minggu. Dosis ditingkatkan secara bertahap hingga 2,0 mg/kg BB dengan lama terapi 1-18 bulan. Semua pasien menunjukkan respon awal yang baik berupa pengurangan massa dan perubahan warna dalam 2-12 minggu. Tidak ada komplikasi dan efek samping yang timbul. Regimen propranolol sistemik 2,0 mg/kg BB dianggap aman dan efektif untuk tatalaksana HKP.

INTRODUCTION

Capillary or infantile hemangioma is the most common congenital vascular tumour of the periorbital region, affecting approximately 5-10% of all infants.[1–3] Hemangioma is a benign tumour of vascular endothelial cells characterised by rapid proliferation during infancy followed by gradual involution.[1,4,5] The natural course of hemangioma has triphasic evolutions: early proliferative, plateau, and involution phase.[6–8]

A periorbital hemangioma could cause significant functional and cosmetic deformities despite its self-limiting nature. Up to 60% of periorbital hemangioma eventually causes amblyopia as a result of astigmatism or mechanical ptosis. It can also lead to proptosis, exposure keratopathy, and compressive optic neuropathy in orbital involvement.[1]

Propranolol, a non-selective beta-blocker, was the most recent addition to modalities in treating infantile hemangioma. It was first reported by Leaute-Lebreze et al. Propranolol showed an inhibitory effect on capillary hemangioma.[9] Although the mechanism of propranolol was not fully understood, several possible mechanisms have been proposed, including vasoconstriction, suppression of angiogenesis, and induction of apoptosis of the endothelial cells.[10,11] Systemic propranolol was highly efficacious in capillary hemangioma with a response rate of 98%.[4,10,11] Possible side effects of systemic propranolol are rare; nonetheless, some studies reported transient hypoglycemia, bradycardia, and hypotension.[12–14] Thus, propranolol is an effective and safe modality for treating capillary hemangioma. We presented five successful cases of infantile hemangioma from our centre in which propranolol was given as chosen management.

CASE DESCRIPTION

Case 1

An 11-month-old infant girl was referred to our hospital with a protrusion of the left eye one month earlier. History of trauma was denied. Ophthalmology examination revealed a bluish palpable mass at the medial side of the globe, causing non-axial proptosis of the left eye and exotropia. Orbital computed tomography scan (CT scan) showed a homogenous mass, which was enhanced with contrast, covering left medial rectus muscle. She was given propranolol orally, starting at 0.5 mg/kgBW. After two weeks of treatment, the dose gradually increased to 2 mg/kg BW. The proptosis started to reduce after one month of therapy. No proptosis was noted within 12 months of therapy, and both eyes looked equal (Figure 1).

Case 2

A 1-month-old infant girl was brought with a complaint of bulging of the right eye presented at birth that has been increasing in size gradually. Ophthalmology examination revealed non-axial proptosis, palpable mass at the inferior of the globe, and lagophthalmos. An orbital CT scan showed an intraorbital homogenous mass that enhanced with contrast. We started propranolol orally at 0.5 mg/kg BW and gradually increased the dose to 2 mg/kg BW. After four months of receiving propranolol therapy, the patient's proptosis was significantly reduced. Furthermore, after seven months of continuing the therapy, the proptosis resolved well. (Figure 2).

Case 3

A 4-month-old infant girl presented with a bluish mass below her lower right eyelid that had been present for one month before admission. She had also had a bluish spot in the same location since birth, which gradually became swollen and enlarged, causing upward displacement of the right globe. During the ophthalmic examination, a non-axial proptosis of the right eye with secondary exotropia was observed. A soft solid mass with an indistinct edge was palpable below the right lower eyelid. An orbital CT scan revealed an intra- and extraconal lesion of the orbit with

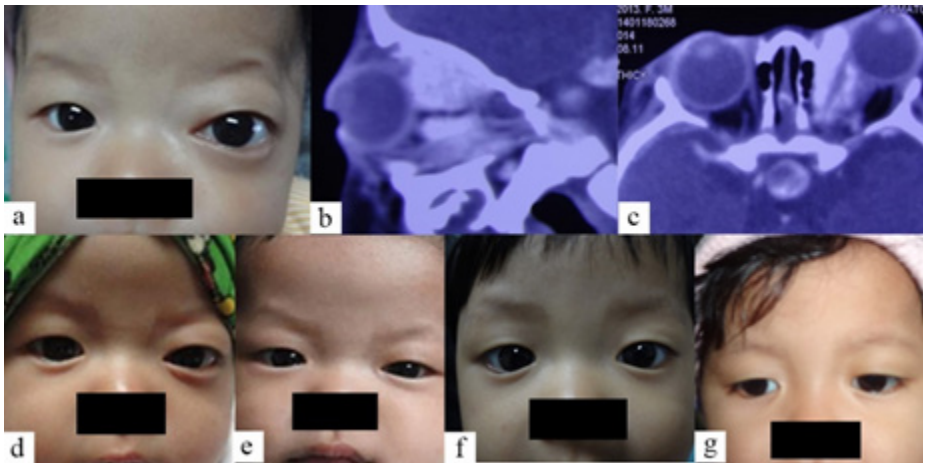

Figure 1. Clinical improvement of case 1 patient. Initial presentation (a); orbital CT scan (b,c); 1 week (d), 1 month (e), 6 months (f), 12 months (g) post propranolol treatment.

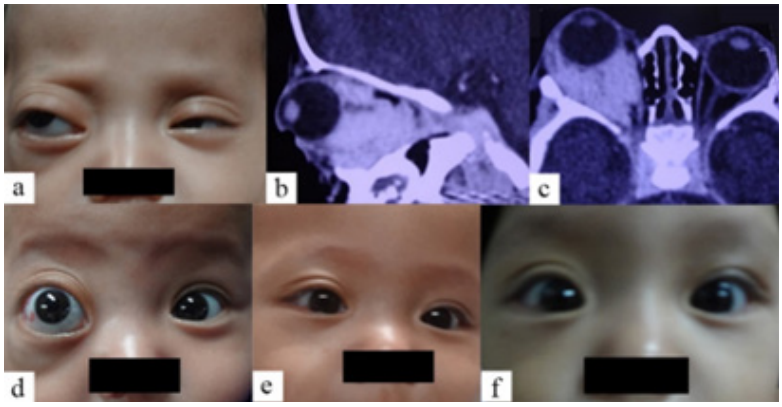

Figure 2. Clinical improvement of case 2 patient. Initial presentation (a); orbital CT scan (b,c); 2 months (d), 4 months (e), 7 months (f) post propranolol treatment.

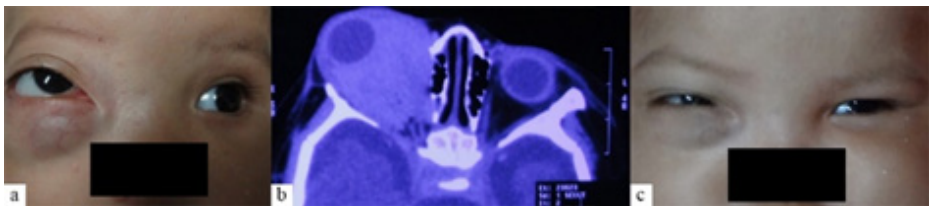

Figure 3. Clinical improvement of case 3 patient. Initial presentation (a); orbital CT Scan (b); 1 month (c) post propranolol treatment

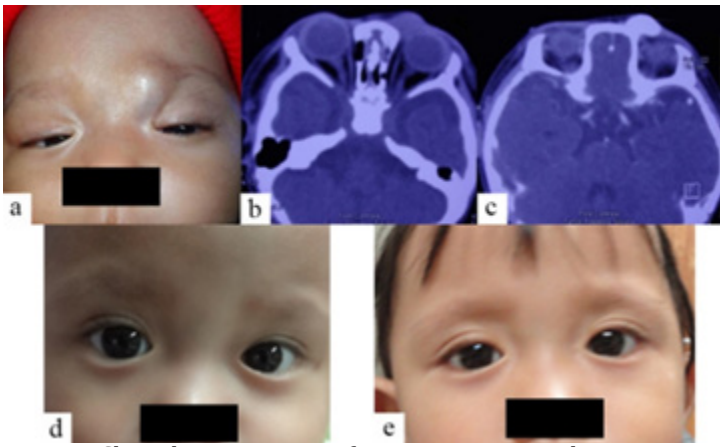

Figure 4. Clinical improvement of case 4 patient. Initial presentation (a); orbital CT scan (b,c); 3 months (d), 8 months (e) post propranolol treatment

contrast enhancement. The patient was orally given propranolol starting at 0.5 mg/kg BW and gradually increased up to 2.0 mg/kg BW. After one month of treatment, the lesion was significantly reduced to approximately half its original size, and the bluish colouration faded. Unfortunately, she was lost to follow-up later on (Figure 3).

Case 4

A 3-month-old infant girl was brought in with a complaint of a bluish mass above her left eyelid that had been enlarging over the past month. On ophthalmologic examination, a tender, well-defined mass measuring 2.4 cm x 3 cm x 1.2 cm was palpable subcutaneously above her left eyelid. A CT scan enhanced with contrast revealed a homogeneous mass that originated subcutaneously above the left orbita. We began treatment with propranolol at 0.5 mg/kg BW and gradually increased the dosage to 1.5 mg/kg BW. After three months of therapy, the mass showed rapid involution, and it fully resolved after eight months of therapy (Figure 4).

Case 5

A 4-month-old infant girl was brought in with a complaint of a painless red lesion on the skin above her left eyelid that had been enlarging over the past two months. The lesion blanched on pressure. We began treatment with propranolol at a dose of 0.5 mg/kg BW and gradually increased the dosage every two weeks up to 2 mg/kg BW. After three months of therapy, we observed gradual regression in size, thickness, and colour. The lesion thinned out, and its colour faded. Therapy was discontinued after 18 months when the lesion became vaguely visible (Figure 5).

DISCUSSION

Capillary or infantile hemangioma is a benign tumour that affects vascular endothelial cells. It can be classified into three types: superficial, subcutaneous, and orbital. The superficial form of hemangioma appears as a bright red, soft mass with a dimpled texture on the skin, commonly referred to as a "*strawberry nevus*". The subcutaneous form appears as a bluish elevation without any visible vascularisation, indicating deep capillary involvement. The orbital form, which typically originates behind the globe, often causes displacement of the globe or proptosis.[5,15] Our first three cases were of the orbital form, the fourth case was of the subcutaneous form, and the fifth case showed the superficial form. All of our patients were female, which is consistent with the literature indicating that females are more likely to be affected.[2,5,16]

The diagnosis of capillary hemangioma is primarily based on clinical evaluation, and no laboratory investigations are currently used to diagnose this condition.[12] However, several ancillary tests, including ultrasound, radiographic imaging, and biopsy, may help assess the extent of periorbital or orbital involvement. Radiographic imaging is often employed to exclude the possibility of more extensive orbital disease. CT scans can identify well-delineated, homogenous tumours that enhance uniformly and display finger-like posterior expansion.[2,12] Magnetic resonance imaging (MRI) may reveal a well-circumscribed, densely lobulated tumour that enhances gadolinium contrast due to the slow blood flow through the vascular channel.[12] In our study, all cases were confirmed as vascular tumours based solely on clinical presentation and imaging, and none of the patients underwent biopsies.

Capillary hemangioma may enlarge or change colour with crying and the cutaneous lesion may blanch with pressure.[12] These findings were consistent with what we found in our cases. All orbital form cases experienced globe displacement as a result of intraorbital lesions. The most common complication in capillary hemangioma is amblyopia due to astigmatism, deprivation, or strabismic due to displacement of the globe.[15,17] The first three cases demonstrated globe displacement, increasing the risk of strabismic amblyopia, whereas the final two cases were susceptible to developing amblyopia caused by mechanical ptosis or astigmatism due to subcutaneous mass

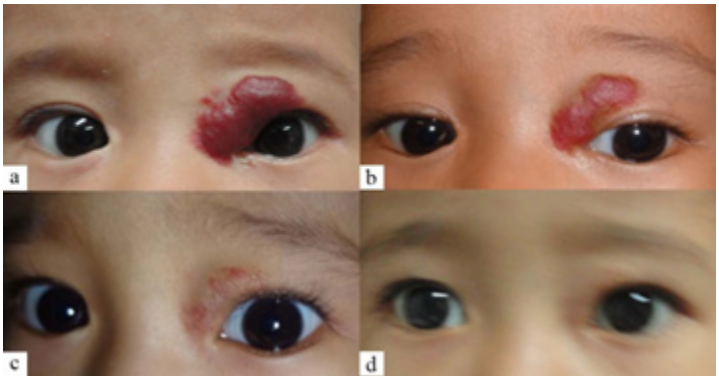

Figure 5. Clinical improvement of case 5 patient. Initial presentation (a); 3 months (b), 9 months (c), 18 months (d) post propranolol treatment

pressure on the eyeball. Considering the visual implications in children, treatment was deemed essential in all cases.

The precise mechanism by which propranolol affects hemangioma remains incompletely understood. Various potential beta-blocker mechanisms have been suggested, including suppression of angiogenesis, vasoconstriction of capillaries, and induction of apoptosis. Capillary hemangioma pathophysiology is believed to originate from beta-adrenoreceptor stimulation by catecholamine, which in turn activates multiple signalling pathways, including angiogenesis through proangiogenic factor expressions like vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP), vasodilation through nitric oxide (NO) formation and release, apoptosis inhibition, decreased gap junction intercellular communication (GJIC), and cell proliferation stimulation.[6,10,11,18] Thus, beta-blockers function by inhibiting catecholamine stimulation, which results in downregulating other proangiogenic factors.

Numerous studies have reported a response rate of up to 90% in most cases when using propranolol. Furthermore, propranolol usage has been shown to significantly reduce amblyopia and astigmatism.[3,17,19-24] All cases displayed a positive response in terms of reducing the mass size and colour changes. The initial response varied among cases, with some showing improvement as early as two weeks after treatment, whereas others required up to three months. Throughout seven to eighteen months after therapy, all five cases exhibited gradual regression until a complete resolution was achieved.

Despite the discovery of propranolol's effectiveness, cautious monitoring of its side effects must be considered with every treatment. Before commencing propranolol therapy, careful tolerance and cardiac assessments by a paediatrician are essential. One study reported that side effects occurred in only 2% of cases, including sleep disturbances, agitation, bronchial hyperreactivity, bronchospasm, and hypoglycemia.[25] Other studies have reported only minor side effects and have considered it to be a safe outpatient management option.[3,16-17,25-28] None of our patients exhibited side effects such as transient hypoglycemia, bradycardia, or hypotension.

CONCLUSION

Capillary hemangioma is a benign vascular endothelial tumour characterised by a self-limiting natural course of the disease. However, most periocular cases, especially those in the orbital form, carry a risk of significant morbidity, making aggressive treatment necessary. Oral propranolol, administered at a dose of 2.0 mg/kg BW, has been concidered safe and effective for treating periocular capillary hemangioma.

CONFLICT OF INTEREST

There is no conflict of interest in this research. The authors are accountable for all aspects of the work in ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian. The authors have obtained appropriate informed consent from the parents as the legal guardian of these patients. The parents have consented to the patient's photo and clinical findings being reported. The parents understand that the patient's name or initial will be enclosed, and efforts to conceal the identity will be made, but anonymity cannot be guaranteed.

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