

Efficacy of Topical β Blockers (0,25% Timolol Maleate Eye Drops[®]) in Treatment of Infantile Hemangioma

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Abstract: Introduction: Infantile hemangioma (IH) is a benign vascular tumor, that occurs several weeks after birth. Pathogenesis of IH considers an escalation of angiogenesis, vasculogenesis in proliferative phases and apoptosis in regression phases. Since 2010, topical timolol maleate has used as a treatment of superficial and non-ulcerated IH. Case: A 2 months 25 days infant admitted to our hospital with a history of bright red swelling on his left forehead. The lesion appeared first like a mosquito bite swelling when the patient was three weeks old, then lesion enlarged and the color became more erythematous. Dermatology examination indicated solitary erythematous nodule, size 0,7x0,3x0,05 cm³, stepping border, and cobblestone surface, rubbery consistency, and warm on left temporal. The hemangioma severity scale (HSS) was six, and hemangioma dynamic complication scale (HDCS) was 0. The patient was treated with topical β blocker timolol maleate eye drop 0,25%[®], one drop twice a day. Three months after treatment, the regression of the lesion was significant with size 0,5x0,1x0,01 cm³. Discussion: Topical β blocker indicated in our case to reduce the risk of functional compromise such as ulceration, scar, and risk for residual skin development include telangiectasia, redundant skin, and fibrofatty tissue after involution phases. Timolol maleate 0,25% 1 drops two times a day resulted in regression of superficial IH, topical and lower concentration used reduces the risk of side effects. Conclusions: Importance to determine the effective treatment for IH based on some points include anatomic depth, morphology, and risk for complication, functional compromise, and permanent disfigurement.

1 INTRODUCTION

Infantile hemangioma (IH) is a benign vascular tumor characterized by increased endothelial proliferation and epidermal turnover. Incidence of IH approximately 5-10%, more common among female infants, with female to male ratios 3:1. Although they occur in all races, IH is more common in Caucasian (Laranjo et al, 2014). Based on a prospective study of IH by Dickson, the risk factors that strongly associated with IH are premature infants, low birth babies (< 2500 gram), babies conceived *in vitro fertilization* (IVF), the family history of IH (62,6%) (Dickison et al, 2011). Pathogenesis of IH have considered an escalation of angiogenesis and vasculogenesis, and upregulated expression of glucose transporter protein type-1 (GLUT-1), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF). GLUT-1 is a specific marker for IH. Two phases of IH

include proliferation and involution. Proliferation occurs several weeks after birth, characterized by quick proliferation of endothelial cell and involution starts by one year of age, characterize by reducing of proliferation, increase apoptosis, and most lesions flatten and shrink from the center outward (Callahan et al, 2012).

Treatment of IH with systemic propranolol first described by Leaute-Labreze *et al.* in 2008, hypothesized mechanisms of action are decreased nitrite oxide, vasoconstriction, blockage of VEGF and FGF, and stimulation of apoptosis causing IH regression (Chambers et al, 2012). Recently, propranolol has become the first-line treatment for complicated IH. Topical timolol maleate as a nonselective β blocker agent, since February 2010, has been reported as treatment of superficial and non-ulcerated IH. Some studies report tumor reduction up to 100% in superficial IH by using timolol maleate 0,5%, 0,25% and propranolol 1%.

Most previous studies described no systemic or only minimal systemic absorption of topical β blocker, but only one report by Weibel *et al.* concluded that topical timolol is systemically absorbed, but the impact of low serum timolol is not well studied (Weibel et al, 2016). Here we report a case of IH that was successfully treated with topical β blocker.

2 CASE

A 2 months 25 days old infant was admitted to our hospital with two months history of bright red swelling on his left forehead. The lesion appeared first like a mosquito bite swelling, with a pale color

on the left forehead when the patient was three weeks old, then lesion enlarged, became more elevated with strawberry-like color. Baby's birth weight was 3,1 kg. Maternal pregnancy history was standard. His father's sister also had the same history as a patient. Physical examination revealed the patient was alert, and other vital signs were typical. There was no abnormality of the airway, cardiovascular, ocular, and motor movements of the patient. The current baby's weight was 5,1 kg. Dermatology examination indicated solitary erythematous nodule with size 0,7x0,3x0,05 cm³, stepping border, and cobblestone surface, rubbery consistency on left forehead. Here is the photo of the patient on the first visit.



Picture 1: Inspection: solitary erythematous nodule, size 0,7x0,3x0,05 cm³, stepping border, cobblestone surface on left temporal. Palpation: Cobblestone surface, rubbery consistency, fixed and warm.

Examination results of IH severity using hemangioma severity scale (HSS) and the risk of IH complication using hemangioma dynamic complication scale (HDCS) indicated:

Table 1. Results of HSS and HDCS

HSS		HDCS	
Parameter	Score	Parameter	Score
Objective items		Infection	0
Size (\leq 1 cm)	1	Ulceration	0
Location (peripheral face)	3	Feeding difficulties	0
Risk for associated structural anomalies	0	Torticollis	0
Complication	0	Cartilage distortion or destruction	0
Subjective items		Airway involvement	0
Pain	0	Visual compromise	0
Risk of disfigurement (telangiectasia)	2	Hypothyroidism	0
		Anemia	0
		Congestive heart failure	0
		GI bleed	0
		Hepatic dysfunction	0
TOTAL	6	TOTAL	0

The table was quoted with a little modification from references number 9 and 10.

Differential diagnoses of this patient are an infantile hemangioma, congenital hemangioma, and

pyogenic granuloma. Clinical diagnosis is infantile hemangioma, and the patient was treated with topical β blocker timolol maleate eye drop 0,25%[®], one drop twice a day. In addition, parents were

educated about a sign of hypothermia, bradycardia, hypotension, hypoglycemia, and encourage them to feed the infant before each dose and do not administer before bedtime without feeding. The progress of this patient was followed monthly by a dermatologist (to see the regression of the lesions) and by a pediatrician (evaluating the cardiopulmonary function and hypoglycemia).

One month after treatment, lesion became smaller and lighter in color with size was

0,7x0,3x0,03 cm³, and the treatment was still continued because there were a good response and no adverse effects. Two months from the first visit, the size of the lesion was regressed, and the size was 0,7x0,03x0,01, and there were no adverse effects detected. Three months from the initial visit, the regression of the lesion was more significant with the current size was 0,5x0,1x0,01 cm³, and there was no adverse effect occurred. Here is the photograph of the patient in the last control:



Picture 2: Inspection: solitary pale erythematous nodule, size 0,5x0,1x0,01 cm³, firm border, pale on left temporal. Palpation: smooth surface, rubbery consistency, fixed and warm nodules

Prognosis of this patient was considered suitable because there were no systemic involvement, no risk of complication or structural anomaly, and permanent disfigurement.

3 DISCUSSION

Infantile hemangioma usually develops on the first 3 or 4 weeks of life. Phases of IH are proliferative and involution. IH proliferate time depending on morphology and configuration. Most growth is completed by around five months. Clinical appearance of IH in proliferative phases is enlargement, elevated, with rubbery consistency, surrounding pallor, and dilatation of surrounding veins. The involution phases range from 1 year until 5-7 years of age, characterize by fading of the shiny crimson color to a dull purplish hue, the surface showed tiny white freckles, lesions softens, affected skin becomes slightly wrinkled (Painter et al, 2019; Moyakine et al, 2019). In our case patient was still in proliferative phases with typically red nodule and rubbery consistency.

Based on lesion distribution and anatomic depth, IH is classified into superficial, deep, and compound type. Superficial IH describes as bright red papules, plaques or nodule which are warm to touch, non-tender with cobblestone or smooth surface, and also known as strawberry type. Deep IH is lesion from

reticular dermis extends to subcutaneous tissues, characterized by blue, appears as flesh-colored to blue masses that are warm to touch. The mixed type has no characteristics of superficial and deep IH. In our cases, the patient showed superficial IH with bright red nodule and warm to touch. Morphological classification of IH is localized, segmental, indeterminate, and multifocal. This classification is often associated with some internal complications and functional compromise. The localized lesion is solitary discrete lesion and typically circular. Segmental IH involves broad anatomic region, often unilateral, and sharply demarcated. Segmental IH has higher rate complication and increases the risk for functional compromise if located on the face, it is often associated with PHACE syndrome, and if it is located on the lumbosacral and anogenital region, is associated with LUMBAR syndrome. Multifocal is numerous lesions (more than 10), discrete, localized lesions present at more than one anatomic sites and often associated with hepatic hemangiomatosis. Indeterminate lesions are not characterized as localized or segmental. (Haggstrom et al, 2019) In our case, this patient has a localized IH with located in temporal region, revealed a solitary nodule with size is less than 1 cm, only superficial involvement based on the erythematous color of the lesion, so there was no risk for complication and functional compromise according to location, morphology and anatomic depth of the lesion.

The score of HSS and HDCS indicate outcome measure, HSS measures the severity of lesion while the HDCS assigns a grade for each complication in a longitudinal use. Complication assessed in HSS is correlated with HDCS grade. Both of the scale measure size changes, complications, and risk for disfigurement. Study of Moyakine in 2017, determined using HSS to facilitate treatment decisions for IH, scores of 11 or higher as a marker for propranolol treatment, scores of 6 or lower as a marker for watchful waiting or topical β blocker treatment, and children with HSS score higher than 6 and lower than 11, treatment decision should consider other factors, including patient age, IH type, and parental preferences. (Zheng et al, 2019; Rotter et al, 2017) In our case, the HSS was six, and HDCS was 0, based on HSS results, the patient was treated with topical β blocker.

Diagnosis IH is based on clinical examination and history. USG, MRI, and CT scan are only required if there is systemic involvement. IH should be differentiated with other vascular anomalies such as congenital hemangioma and pyogenic granuloma. This lesion occurred three weeks after birth, and the lesion was rapidly progressed to eliminate the diagnosis of congenital hemangioma. Location on the face, tumor with red to brownish red color manifested in pyogenic granuloma and IH, but because in our case the lesion occurred several weeks after birth and the surface of the lesion was not easily bleeds and ulcerated, favor diagnosis as IH. Treatment of IH has a purpose of preventing complication, functional compromise, and permanent disfigurement for this patient. In our case, the lesion was superficial and localized, so the primary purpose of administered treatment for this patient was to reduce the risk of functional compromise such as ulceration and scar and risk for residual skin development include telangiectasia, redundant skin, and fibrofatty tissue after involution phases. Previous studies reported most 0,5% topical timolol maleate, administered one drop two times a day resulted in complete regression of superficial IH, but only a few studies reported the use of lower concentration (timolol maleate 0,25%) with the same potential to reduce the lesion. Lower concentration theoretically further reduce the risk of side effects, such as hypotension, hypoglycemia, bradycardia, and bronchoconstriction. (Chambers et al, 2012).

Prior before starting treatment, we examined complete blood count (include blood glucose), cardiovascular function, and pulmonary function. Laboratory test and cardiopulmonary were regular so that we started the treatment with topical β

blocker. Contraindication for β blocker includes AV block (grade 2 and 3), congestive heart failure, bronchospasm, hypoglycemia, hypotension, and sinus bradycardia. Topical timolol maleate 0,5% solutions or GSF consider safe treatment for superficial IH in term infants receiving a dose less than 0,2 mg/kg/day, with no adverse events reported. Higher risk for systemic adverse events is prematurity and low birth weight, baby. Adverse events of β blocker usually reported by using systemic propranolol, but only a few or almost no adverse event reported by using topical β blocker. Short-term adverse events include hypotension, bradycardia, and hypoglycemia. Long-term adverse events include emotional lability, sleep disturbance, and other effects related to neural depressant effects. In our case, the patient was a term baby with average birth weight, and the lesion was superficial, non-ulcerated, and located in the temporal region so that the risk for systemic complication consider minimal or none. Topical application of β blocker have a higher risk for systemic complication if given on mucosal surface (ocular, lips, anogenital), ulcerated IH, and extend large IH. Evaluation of possible systemic complication accomplished by educating parents to evaluate sign and symptoms of adverse events include lethargy, cyanosis, mottled/cold skin, irritable, tremor, and excessive sweating. Monthly evaluation of cardiopulmonary function and blood glucose checks in hospital. In our case, during three months of treatment, there were no adverse effects occur.

4 CONCLUSIONS

This case represents the treatment of superficial non-complicated successfully, and non-ulcerated IH with topical β blocker timolol maleate 0,25% eye drops[®]. There were no adverse effects reported in this case. It suggests an important to determine the effective treatment for IH based on some points, include anatomic depth, morphology, and risk for complication, functional compromise, and permanent disfigurement. The purpose of initial administration treatment for superficial IH consider to reduce the risk of functional compromise such as ulceration and scar and risk for residual skin development include telangiectasia, redundant skin, and fibrofatty tissues.

REFERENCES

- Callahan AB, Yoon MK. 2012. *Infantile Hemangiomas: A Review*. *AAO* [internet]. [cited 2019 January 29];26:283-91. Available from: https://www.researchgate.net/publication/255987798_Infantile_hemangiomas_A_review DOI: 10.1016/j.sjopt.2012.05.004
- Chambers CB, Katowitz WR, Katowitz JA, Binenbaum G. 2012. A Controlled Study of Topical 0,25% Timolol Maleate Gel for the Treatment of Cutaneous Infantile Capillary Hemangiomas. *Ophthal Plast Surg* [internet]. [cited 2019 February 16]; 28(2): 103-6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22410658>doi:10.1097/IOP.0b013e31823bfff8
- Dickison P, Student M, Christou E, Wargon O. 2011. A Prospective Study of Infantile Hemangiomas with a Focus on Incidence and Risk Factors. *Pediatr Dermatol* [internet]. [cited 2019 February 20]; 28(6): 663-9. Available from: www.ncbi.nlm.nih.gov/pubmed/21995808doi:10.1111/j.15251470.2011.01568.
- Haggstrom AN, Beaumont JL, Lai SL, Adams DM, Droet BA, Frieden IJ, *et al.* 2012. Measuring the Severity of Infantile Hemangiomas. *Arch Dermatol* [internet]. [cited 2019 January 30]; 148(2):197-202. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22351819> doi: 10.1001/archdermatol.2011.926.
- Laranjo S, Costa G, Parames F, Freitas I, Martins JD, Trigo C, *et al.* 2014. The role of propranolol in the treatment of infantile hemangioma. *Rev Port Cardiol* [internet]. [cited 2019 January 28];33(5):289-95. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24906291> doi:10.1016/j.repc.2013.10.018
- Moyakine AV, Kouilil S, Vleuten CJM. 2017. Propranolol treatment of infantile hemangioma is not associated with psychological problems at 7 years of age. *J Am Acad Dermatol* [internet]. July. [cited 2019 January 29];105-8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28190620> doi: 10.1016/j.jaad.2017.01.025.
- Moyakine AV, Herwegen B, Vleuten CJM. 2017. Use of the hemangioma Severity Scale to facilitate treatment decisions for infantile hemangiomas. *J Am Acad Dermatol* [internet]. August 14. [cited 2019 January 30];77(5):868-73. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28818436>doi: 10.1016/j.jaad.2017.06.003
- Painter SL, Hildebrand GD. 2016. Review of topical beta blockers as treatment for infantile hemangiomas. *Surv Ophthalmol* [internet]. [cited 2019 January 29];61:51-8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26408055> doi: 10.1016/j.survophthal.2015.08.006.
- Paller AS, Mancini AJ. 2016. *Hurwitz Clinical Pediatric Dermatology*. Fifth edition. [cited 2019 February 3]. Chicago: Elsevier. pp: 279-95.
- Rotter A, Najjar Z, Oliveira P. 2017. Infantile hemangiomas: pathogenesis and mechanisms of action of propranolol. *JDDG* [internet]. [cited 2019 January 29];1185-1190. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29193649> doi: 10.1111/ddg.13365
- Weibel L, Barysch MJ, Scheer HS, Konigs I, Neuhaus K, Schiestl C, *et al.* 2016. Topical Timolol for Infantile Hemangiomas: Evidence for Efficacy and Degree of Systemic Absorption. *Peadr Dermatol* [internet]. [cited 2019 February 7]; 33(2):184-90. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26840644> doi: 10.1111/pde.12767.
- Zheng JW, Zhou Q, Mai HM, Wang YA, Fan XD, Qin ZP. 2013. A practical guide to treatment of infantile hemangiomas of the head and neck. *Int J Clin Exp Med* [internet]. [cited 2019 January 31];6(10):851-60. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24260591>