

## Topical Beta Blockers in Small Infantile Hemangioma: State of the Art?

Bittmann S\*, Moschüring-Alieva E, Bittmann L, Luchter E, Villalon G

### Introduction

Infantile hemangiomas (IH) are benign forms of endothelial proliferation in the first 8 weeks of life [1-11]. Leaute-Labreze et al. published the first spontaneous cases of IH treated with beta blockers in 2008 due to their cardiac disease in the New England Journal of Medicine. This was a revolutionary new understanding of treatment in infantile hemangioma (IH). Not only systemic but also topical beta blockers seem to be an effective treatment option for small infantile hemangioma. Efficacy and safety of topical beta blockers in the treatment of infantile hemangioma (IH) were proved in systematic reviews and meta-analysis [11].

We present the cases of two children with infantile superficial hemangiomas (IH) treated in our pediatric department. Both parents signed a written consent document to prepare treatment of 2 patients with topical timolol as different studies and clinical analysis have recommended the „off-label“ treatment of topical timolol for infantile hemangiomas with great success [1-4, 6-11].

### Case Report

Topical timolol, in a concentration as 0.5% gel, was applied on the hemangioma surface in the morning and the evening put it carefully on the hemangiomal surface. This method was performed for the period of two weeks in each patient. Before start of the therapy, photo documentation of both hemangiomas were taken (Picture A and C). After two weeks, the children were observed for a follow-up and once again, photo documentation was taken (Picture B and C). We observed a clearly-visible change in color from fully red to shade grey

and partially color similar to skin color; the skin impressed with a palpable softness of the hemangiomal surface.

**Figure A:** Patient 1 before treatment with topical timolol.



Department of Pediatrics, Ped Mind Institute (PMI), Gronau, Germany

\*Corresponding Author: Stefan Bittmann, Head of the Department of Pediatrics and Ped Mind Institute (PMI) Pediatrician, Hindenburgring, Gronau, Germany.

Accepted Date: 22-04-2021

Published Date: 22-05-2021

Copyright © 2021 by Bittmann S. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Figure B:** Patient 1 after two weeks of therapy with topical timolol.



**Figure C:** Patient 2 before treatment with topical timolol.



**Figure D:** Patient 2 after two weeks of therapy with topical timolol.



Blood pressure and heart rate were normal and no complications were found or reported by the parents at home and the examination of both children was without any new aspects, which impresses to finish the local beta blocker therapy.

### Discussion

Infantile hemangiomas occur in 5 to 10% of children and are the most common benign soft tissue tumors in childhood. Most hemangiomas resolve spontaneously and only a few require systemic treatment, e.g. B. with beta blockers or interferon. 10% of

infantile hemangiomas must be treated during the proliferative phase [5], especially in the first year of life, as local complications such as ulceration, bleeding and necrosis can lead to scars that are difficult to repair cosmetically in later life. The hemangiomas can even lead to deformities if they are located in the area of the lip, the tip of the nose or the ear. Therefore, early treatment and therapy is of the utmost importance.

Propranolol, a non-selective beta blocker, has been shown to be an effective treatment compared to corticosteroids. The therapeutic effects of propranolol in infantile hemangiomas are the vasoconstriction of the vascular tissue, the reduced expression of the genes of the vascular endothelial growth factor (VEGF) and the basic fibroblast growth factor (bFGF) by downregulating the RAF / mitogen-activated protein kinase pathway as well as the apoptosis of the capillary endothelial cells inside the hemangioma [1].

In a meta-analysis done by Khan et al. in 2017, the treatment with topical timolol 0.5 % was well tolerated and authors came to the result, that topical timolol is an effective treatment in infantile hemangioma. Nevertheless, there is at the moment a very small guidance of optimal dosage and time of application [11].

Timolol is very similar to propranolol. It is available as a topical gel for the treatment of glaucoma in both children and adults. Our cases and multiple studies before suggest that topical timolol gel is effective and safe for the treatment of infantile hemangiomas, and is a viable alternative to systemic propranolol for smaller hemangiomas [6-11]. Further prospective

studies are needed to determine the efficacy and safety of timolol maleate, 0.5% gel in the treatment of hemangiomas.

## References

1. Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. *Arch Dermatol.* May;146(5):564-5.
2. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med.* 2008 Jun 12;358(24):2649-51.
3. Khunger N, Pahwa M. Dramatic response of a large hemifacial infantile hemangioma associated with PHACE syndrome to topical timolol lotion. *Br J Dermatol.* Dec 15.
4. Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using beta-blocker solution. *Arch Ophthalmol.* Feb;128(2):255-6.
5. Enjolras O, Gelbert F. Superficial hemangiomas: associations and management. *Pediatr Dermatol.* 1997 May-Jun;14(3):173-9.
6. Harter N, Mancini AJ. Diagnosis and Management of Infantile Hemangiomas in the Neonate. *Pediatr Clin North Am.* 2019 Apr;66(2):437-459. doi: 10.1016/j.pcl.2018.12.011. PMID: 30819347.
7. Püttgen K, Lucky A, Adams D, Pope E, McCuaig C, Powell J, Feigenbaum D, Savva Y, Baselga E, Holland K, Drolet B, Siegel D, Morel KD, Garzon MC, Mathes E, Lauren C, Nopper A, Horii K, Newell B, Song W, Frieden I; Hemangioma Investigator Group. Topical Timolol Maleate Treatment of Infantile Hemangiomas. *Pediatrics.* 2016 Sep;138(3):e20160355. doi: 10.1542/peds.2016-0355. Epub 2016 Aug 15. PMID: 27527799.
8. Zheng L, Li Y. Effect of topical timolol on response rate and adverse events in infantile hemangioma: a meta-analysis. *Arch Dermatol Res.* 2018 May;310(4):261-269. doi: 10.1007/s00403-018-1815-y. Epub 2018 Jan 23. PMID: 29362868.
9. Frieden IJ, Püttgen KB, Drolet BA, Garzon MC, Chamlin SL, Pope E, Mancini AJ, Lauren CT, Mathes EF, Siegel DH, Gupta D, Haggstrom AN, Tollefson MM, Baselga E, Morel KD, Shah SD, Holland KE, Adams DM, Horii KA, Newell BD, Powell J, McCuaig CC, Nopper AJ, Metry DW, Maguiness S; Hemangioma Investigator Group. Management of infantile hemangiomas during the COVID pandemic. *Pediatr Dermatol.* 2020 May;37(3):412-418. doi: 10.1111/pde.14196. Epub 2020 May 16. PMID: 32298480; PMCID: PMC7262142.
10. Koh SP, Leadbitter P, Smithers F, Tan ST.  $\beta$ -blocker therapy for infantile hemangioma. *Expert Rev Clin Pharmacol.* 2020 Aug;13(8):899-915. doi: 10.1080/17512433.2020.1788938. PMID: 32662682.
11. Khan M, Boyce A, Prieto-Merino D, Svensson Å, Wedgeworth E, Flohr C. The Role of Topical Timolol in the Treatment of Infantile Hemangiomas: A Systematic Review and Meta-analysis. *Acta Derm Venereol.* 2017 Nov 15;97(10):1167-1171. doi: 10.2340/00015555-2681. PMID: 28421234.