



DERMATOLOGY ДЕРМАТОЛОГИЯ

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CLINICAL CASE
КЛИНИЧЕСКИЙ СЛУЧАЙ

Topical timolol maleate in the treatment of mixed and deep infantile hemangiomas: a report of two cases

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Abstract. *Relevance.* Infantile hemangiomas are the most prevalent vascular tumors in children. Since the natural progression of infantile hemangiomas is typically benign, over 90 % of cases do not require medical intervention. However, treatment is necessary for infantile hemangiomas that present local complications, functional impairments, or a risk of disfigurement. In this article we presented two children with mixed and deep infantile hemangiomas, with satisfactory therapeutic responses after treatment with topical timolol maleate. *Conclusion.* Timolol maleate is an effective, well-tolerated, and safe treatment option for various types of infantile hemangiomas.

Keywords: hemangioma, timolol, propranolol, topical, treatment

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Conflict of interest statement: The authors declare no conflict of interest.

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Introduction

Infantile hemangiomas (IHs) are vascular neoplasms and the most common soft tissue tumors of infancy, characterized by aberrant blood vessel architecture and abnormal proliferation of endothelial cells, occurring in about 5 % of infants [1]. Most IHs do not require treatment, but 5–10 % of patients with IHs require some form of intervention. Although there is no algorithm to determine the most appropriate intervention for IHs, treatment should be individualized based on the patient's age, the size and growth phase of the lesions, morphology, location, the presence or possibility of complications, and the urgency of intervention [1, 2].

We present the therapeutic effects observed in two infants with a single cutaneous IHs, who were treated with topical timolol maleate. Timolol maleate, in the form of a 0.5 % gel, was applied twice daily directly to the IHs, while avoiding the surrounding skin. We evaluated the effectiveness of timolol therapy using the Hemangioma Activity Score (HAS) before treatment initiation and again after 6–7 months [3]. The photographs were taken at different points in time, before as well as during the usage of topical timolol therapy.

Clinical report

Patient 1. The 3-month-old girl had a mixed IH on her right upper eyelid, causing blepharoptosis and almost covering her pupil. The IH was oval, measuring 17×10 mm in diameter. It was reddish-purple in color and elevated about 2 mm above the surrounding skin at its central part, with a HAS score of 9 (Figure 1).



Fig. 1. Mixed infantile hemangioma on the right upper eyelid before topical timolol therapy

The infant's parents were concerned about the IH, worrying about its enlargement and potential adverse medical and aesthetic effects. We treated the IH for six months with topical timolol maleate, advising additional eye protection. After that period, the treated IH was flattened almost to the level of the surrounding skin, and its surface was similar in color to the surrounding area (HAS score 2) (Figure 2).



Fig. 2. Infantile hemangioma on right upper eyelid after six months of usage of topical timolol therapy

Patient 2. The 2.5-month-old boy had a deep IH at the top of his head, on the left side of the sagittal suture, with no evident surface changes (Figure 3).



Fig. 3. Deep infantile hemangioma at the top of the head before timolol therapy

It had a regular ovoid shape, measured ultrasonographically at 23×19×3.7 mm, above the surrounding skin, and its HAS score was assessed at 6 (Figure 4).

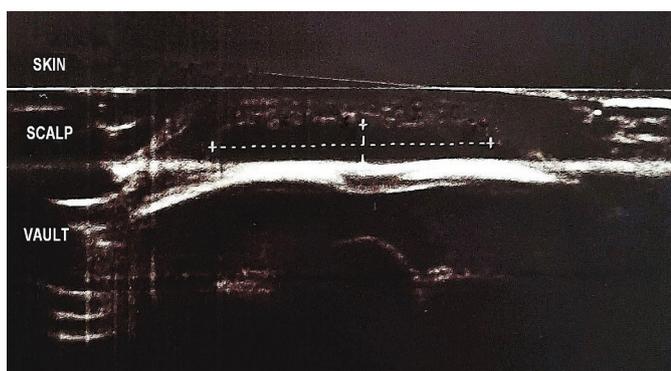


Fig. 4. A well-defined, deep, ovoid lesion which measures 23 x 19 x 3.7 mm is seen in the subcutaneous plane

After seven months of local therapy with 0.5% timolol maleate gel, the IH completely disappeared, the skin color was normal, and the HAS score dropped to 0 (Figure 5).



Fig. 5. Infantile hemangioma at the top of the head after seven months of topical timolol therapy

Discussion

There are many modalities of therapy for IHs, including non-selective β -blockers (propranolol and topical timolol), corticosteroids, interferon- α , imiquimod, anti-angiogenic agents, physical measures (laser surgery, cryosurgery), and surgical interventions in select patients [1].

Currently, beta-blockers are considered the first-line therapy for different types of IHs, with other treatment options becoming less necessary after this discovery. The mechanism of action involves several pathways contributing to the regression of these vascular tumors. These pathways induce vasoconstriction of blood vessels and reduce nitric oxide release, block proangiogenic signals, prevent the secretion of proteases necessary for reorganization into functional vessels (angiogenesis), and induce apoptosis [4].

Due to propranolol affecting the cellular physiology of IHs endothelial cells across the vessels, while topical timolol maleate interacts with hemangioma pericytes circumscribing the vessels, Wu HW et al. hypothesized that local timolol maleate and systemic propranolol might exert their effects partly by targeting different cells [5]. The same authors compared the efficacy and safety of propranolol and topical timolol maleate, concluding that topical timolol is at least as effective as oral propranolol for the treatment of superficial IHs, with success rates of 97% and 96.4%, respectively. Püttgen et al. conducted a multicenter retrospective cohort study involving 731 patients who were treated with timolol maleate for IHs. The study found that only 7.3% of these patients required subsequent therapy with systemic β -blockers [6].

Adverse effects are more frequently observed with systemic beta-blockers compared to topical application. Oral propranolol in the pediatric population can lead to sleep disorders, somnolence, agitation, hypotension, bradycardia, pulmonary symptoms, hypoglycemia, and gastrointestinal symptoms [7].

Timolol maleate is a relatively new therapy for IHs with no statistically significant side effects, although some studies have raised concerns about systemic absorption and potential side effects such as sleep disturbances [2]. Chakkittakandiyl et al. performed

a retrospective, multicenter study, including 73 children with IHs [8]. Only one patient experienced systemic side effects (sleep disturbance). We did not observe any side effects in our two patients.

A 2018 Cochrane review, comprising 28 randomized controlled trials and 1,728 patients, compared various treatments for IHs. The authors concluded that topical timolol maleate was as effective as oral propranolol based on one study involving 26 participants (very low-quality evidence) [9].

Consensus statements from the Australasian Vascular Anomalies Network and the Australasian Paediatric Dermatology Network, as well as the American Academy of Pediatrics, British Society for Pediatric Dermatology, and European expert group, all recommend oral propranolol as the treatment of choice for IHs [1, 10–12]. However, except for the British Society for Pediatric Dermatology, these consensus guidelines also include topical timolol maleate as a possible early treatment option only for small and superficial IHs. This recommendation is based on evidence rated as not high-quality and mainly derived from a small number of patients. Both the American Academy of Pediatrics and European expert groups mention topical timolol maleate, noting that only one randomized controlled trial has compared it to a placebo.

Conclusion

In conclusion, current consensus guidelines justify the application of topical timolol maleate as an effective treatment for small and superficial IHs. Furthermore, our findings suggest that timolol maleate may also be an effective and safe treatment option for reducing the volume of not only superficial IHs but also deep or mixed IHs in the outpatient setting.

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Местное применение тимолола малеата в лечении смешанных и глубоких младенческих гемангиом: сообщение о двух случаях

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Аннотация. *Актуальность.* Инфантильные гемангиомы являются наиболее распространенными сосудистыми опухолями у детей. Поскольку естественное развитие инфантильных гемангиом обычно доброкачественное, более 90 % случаев не требуют медицинского вмешательства. Однако лечение необходимо для инфантильных гемангиом, которые представляют местные осложнения, функциональные нарушения или риск обезображивания. Мы представили двух детей со смешанными и глубокими инфантильными гемангиомами с удовлетворительными терапевтическими ответами после лечения топическим тимололом малеатом. Выводы. Тимолол малеат является эффективным, хорошо переносимым и безопасным вариантом лечения различных типов инфантильных гемангиом.

Ключевые слова: гемангиома, тимолол, пропранолол, местный, лечение

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