

Topical timolol for small infantile hemangioma: a new therapy option

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The main characteristic of infantile hemangioma is that it grows rapidly after birth and mostly regresses spontaneously. It is a common practice for only a small part of the hemangioma to be treated, as they can be extremely disfiguring and destructive to normal tissue as well as possibly being life-threatening. Recent studies have discovered that the use of topical 0.5% timolol maleate gel is a new therapy option for infantile hemangioma.

We have treated two children with hemangioma in our pediatric day center with topical timolol gel (Nyogel). We examined the children before the therapy and took photographs of the hemangioma. After a period of two weeks, pictures were re-taken and compared. A significant change in color from dark red to a lighter shade of red and partially even to skin color could be detected. The treatment outcome of our cases indicates that timolol gel is well-tolerated and effective for the therapy for infantile hemangioma. We further want to highlight the necessity to treat even small hemangiomas, as a reliable prediction of the possible extent of the expansion and involution does not exist.

Key words: topical timolol, children, infantile hemangioma.

Infantile hemangiomas occur in 5% to 10% of light-skinned children and they are the most-common soft-tissue tumors of infancy¹. They occur with an incidence of 10% to 12% within the first year of life, and female infants are three to four times more likely to suffer from hemangioma as male infants². Hemangiomas are neoplastic proliferations of endothelial cells, which grow after birth and regress spontaneously³, and only a few need to be treated systemically. It is a common practice that 10% of the infantile hemangiomas are treated during the proliferative phase as local complications, such as ulceration, hemorrhage and necrosis, which can lead to scars that are difficult to repair⁴. Hemangiomas can lead to deformities when they are located in the areas of the lip, nasal tip or the ear, and they can even be life-threatening when present in the upper airways and liver, by inducing acute respiratory failure and congestive heart failure.

For the therapy of infantile hemangiomas, propranolol, a non-selective beta blocker, has proven to be an effective alternative to

corticosteroids, which have many potential side effects. The suspected therapeutic effects of propranolol in infantile hemangiomas are vasoconstriction, decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) genes by down-regulating the RAF/mitogen-activated protein kinase pathway, and the apoptosis of capillary endothelial cells⁵.

Timolol, also a non-selective beta blocker and similar to propranolol, is available as a topical gel for the treatment of glaucoma. Several studies indicate that topical timolol gel is effective and safe for the treatment of infantile hemangiomas and is a real alternative to systemic propranolol^{6,7}. Preliminary results indicate that topical timolol is effective not only in stopping hemangioma growth, but also causes decreased tumor volume with more regularity than corticosteroids.

Material and Methods

Two children with infantile superficial hemangioma presented to our pediatric day

center at the age of 5 and 6 months. In one child, the hemangioma was located on the lower back, measuring about 10 mm in length and 6 mm in width. The other child had a superficial hemangioma on the right side of his head, measuring about 11 mm in length and 7 mm in width. With the written consent of both parents, we treated both children with 0.1% timolol maleate gel. A physical examination of the children was performed before the start of the therapy in order to exclude other illnesses and rule out treatment contraindications. Furthermore, an electrocardiography was performed and blood pressure was taken. Neither child received systemic or other topical medication, and there were no contraindications; they were healthy and showed normal results.

Results

Timolol gel was applied twice a day by rubbing carefully on the hemangioma, for a period of two weeks. Before the start of the therapy, pictures of the hemangioma were taken. After two weeks, the parents presented their children for a follow-up and pictures were taken again. The pictures were presented to two independent pediatricians with the request for an objective assessment. Both pediatricians confirmed a significant change in color from dark red to a lighter shade of red and partially even to skin color. The pediatricians independently stated that an improvement toward the disappearance of the hemangiomas could be detected.

No side effects were reported by the parents, and the follow-up examinations of both children, which also included an electrocardiography as well as a measurement of blood pressure, were unremarkable. A further therapy with timolol gel under the close surveillance of a physician is planned for a period of four months or until the hemangioma disappears.

Discussion

We treated two children with superficial hemangioma over a short period of time considering the slow disappearance without therapy, and an improvement could already be detected after two weeks. The growth of a hemangioma can be categorized in three phases as proliferation, starting in the first

weeks of life and continuing over the first months, the early involution, starting mostly after the first year of life and continuing over the next years, and the late involution, which takes places around adolescence⁸. Our children presented with relatively small hemangiomas; however, especially in small lesions, a therapy should be indicated since no reliable factors exist that might help to predict the duration of the proliferative phase. It is extremely difficult to assess whether a hemangioma will continue growing or regress spontaneously. In addition, the involution phase is very slow and might take even years, and in one-third of the cases, there are residual findings with de- or hyperpigmentation, excess skin, destruction, or a scar. As a result, even the treatment of small hemangioma should be considered as a regular therapy, as it is not possible to predict the outcome. In our cases, a significant improvement could be detected after only two weeks, and considering the very long physiological involution phase, the improvement must be due to the timolol gel treatment.

Other authors have also discovered the positive effect of timolol gel in a small study group. Guo et al.⁶ described a case of one child with a capillary hemangioma of the eyelid treated with β -blocker solution; Pope et al.⁵ described a series of six children, and Ni et al.⁹ described seven cases of children with superficial capillary hemangioma of the eyelid. All children were treated successfully with timolol gel, and no side effects occurred in these studies. However, Lawley and Siegfried¹⁰ reported on side effects of systemic propranolol, such as hypoglycemia, bradycardia and hypotension. As timolol is quite similar to propranolol, the systemic effects on children remain unclear, despite the fact that we used timolol topically.

On the other hand, these children were not all treated in a prospective, controlled fashion, and therefore the use of topical timolol gel should be regarded with caution, as many questions concerning the efficacy and safety remain to be clarified. It is evident that one cannot conclude from only two cases a general treatment regimen for all children with infantile hemangiomas, as in order to obtain clear treatment recommendations, a double-blind, placebo-controlled study with a larger

population is needed. However, it is known that for children at this age, it is difficult to obtain the permission from both parents and an ethics commission. Therefore, before undergoing the long process of conducting a randomized controlled trial, many different observational studies with a few cases are extremely helpful in order to gain more experience in this interesting field.

It is very important to underline the need for caution with the off-label use of timolol gel in the treatment for infantile hemangioma. Nevertheless, under the careful surveillance of a pediatrician, the positive effects of timolol gel on infantile hemangiomas are evident, and it may soon be regarded as the standard therapy option.

In conclusion, timolol gel is an effective therapy option for infantile hemangioma, and should also be considered as a regular treatment for smaller lesions, as the extent of the expansion and involution cannot be predicted. To date, only observational studies exist; prospective studies with a larger study population are needed in order to establish the exact role of timolol gel in the treatment of infantile hemangioma.

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