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Case report/Kazuistyka

Topical timolol gel for the treatment of residual facial hemangioma previously treated with propranolol

Timolol w leczeniu miejscowym resztkowego naczylniaka twarzy leczonego uprzednio propranololem

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ABSTRACT

This case report demonstrates efficacy of topical timolol for the treatment for residual IH in the facial area in a child, previously treated with propranolol. The treatment was well tolerated. Local or systemic side effects were not seen. **Conclusion:** Timolol gel is an effective therapy option for residual hemangiomas, and should be considered as a complementary treatment for residual hemangiomas after terminating propranolol treatment.

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Introduction

Infantile hemangiomas (IH) are neoplastic proliferations of endothelial cells, which grow after birth and usually regress spontaneously [1]. IH occur with an incidence of 10–12% within the first year of life, and female infants are three to four times more likely to suffer from IH as male infants [2]. IH can lead to deformities when they are located in the facial areas of the lip, nasal tip or the ear. IH can be life-threatening when present in the upper airways, brain and liver, by inducing acute respiratory failure and congestive heart failure [1, 2]. Tumor involvement can be superficial, deep, or mixed. The majority of IH enlarge over 6–9 months and then spontaneously involute over 2–10 years. It is difficult to assess whether IH will continue growing or regress spontaneously. Often there are residual findings [1, 2]. Although the majority of residual IH are aesthetically insignificant, but still may be the cause of parents concern if in visible locations. The treatment of even small hemangioma in the facial area should be considered, as it is not possible to predict the outcome, and they are associated with parental distress. Currently there are not many therapeutic options. Corticosteroids have been the first-line agents for systemic treatment for IH. Recently oral propranolol, a non-selective beta-blocker, has emerged as an alternative in the treatment of IH [1, 2]. Corticosteroids and propranolol both may have significant systemic adverse effects [3, 4]. A limited number of topical agents have been adapted for treatment of IH – corticosteroids and imiquimod [5]. Small IH were also treated by pulse dye laser (PDL) [5]. Recently, timolol maleate gel, a topical nonselective beta-blocker has been reported as a potential new topical agent for superficial IH [6]. We present a case report of multisite, facial, superficial IH treated with propranolol and its residual treated successfully with timolol maleate gel.

Case report

A baby girl with multiple, facial hemangiomas presented to our department at the age of 2 months. The hemangiomas were superficial and located on the eyelids, on the tip of the nose, on the upper lip and in the temporal area of the forehead (Fig. 1). A physical examination of the girl was performed before the start of the therapy in order to exclude other illnesses and rule out treatment contraindications. An echocardiography was performed and blood pressure was taken. With the written consent of both parents, at the beginning the girl was treated with propranolol. During three consecutive days dosage of propranolol was gradually increased to 3 mg/kg. During ambulatory surveillance of the girl, potassium, sodium, chlorine, glucose, liver enzymes, morphology, vital signs and ECG were monitored. The hemangiomas slowly diminished in size. After 6 months of treatment the dose of propranolol was reduced to 2 mg/kg. After next 2 months of treatment the dose was reduced to 1 mg/kg. The treatment was terminated after 10 months at the age of 1 year. Still there were residual hemangiomas on the upper lip, tip of the nose and forehead, and were the



Fig. 1 – Patient before the treatment
Ryc. 1 – Pacjent przed leczeniem

cause of parents concern (Fig. 2). At the age of 1 year and 3 months the treatment with timolol maleate gel was started. Timolo gel was applied twice a day by rubbing carefully on the hemangiomas, for a period of 2 months, and once a day for a period of one month. Before the start of the timolol therapy, pictures of the hemangiomas were taken. No side effects were reported by the parents, and the



Fig. 2 – Patient after oral propranolol treatment
Ryc. 2 – Pacjent po doustnym leczeniu propranololem



Fig. 3 – Patient after topical treatment with timolol
Ryc. 3 – Pacjent po miejscowym leczeniu timololem

follow-up examination of the girl, which included electrocardiography as well as a measurement of blood pressure, were unremarkable. After three-month treatment the result was excellent (Fig. 3). Response to timolol treatment was stable over time. After one year surveillance, at the age of 2.5 year there are no traces of facial hemangiomas in our patient.

Discussion

In 2008, Leaute-Labreze et al. reported the incidental finding that IH regress in children treated with propranolol, a nonselective beta-blocker used in treating infants with cardiac and renal conditions [7]. In most case reports, propranolol was not used as a single therapy of IH, patients received concomitant systemic or intralesional steroids and laser treatment [8]. Schiestl et al. in their study included only infants with IH treated exclusively with propranolol at a dose of 2 mg/kg/day, and in all patients there was a significant cosmetic improvement [9].

The effect of propranolol on IH can be attributed to molecular mechanisms: vasoconstriction, decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) genes through the down-regulation of the RAF-mitogen-activated protein kinase pathway, inhibition of angiogenesis, and induction of apoptosis [9]. Treatment with propranolol may cause severe systemic complications and infants need to be closely monitored [1, 2, 4, 5, 7-9]. During propranolol therapy of our patient, potassium, sodium, chlorine, glucose, liver enzymes, morphology, vital signs and ECG were monitored. The most common reported side effects of propranolol include hypotension, bradycardia, hypoglycemia and bronchospasm [1, 2, 4, 5, 7-9]. Moreover propranolol may mask the clinical signs of early cardiac failure, diminish cardiac performance, and blunt clinical features of hypoglycemia. Prolonged hypoglycemia in infancy is associated with neurologic sequelae [1]. During ambulatory surveillance we did not observe hypoglycemia, hypotension or adverse cardiac effects. The treatment was well tolerated.

For small, superficial IH treatment options are: intralesional steroids, PDL treatment, topical steroids, imiquimod 5% cream and topical propranolol hydrochloride or timolol maleate [6].

Several studies indicate that topical timolol gel is effective and safe for the treatment of IH and can be an alternative or complementary to systemic propranolol [10]. Topical timolol is effective not only in stopping hemangioma growth, but also causes decreased tumor volume [10].

Guo and Ni were the first who reported the positive effects of the use of topical timolol in treating capillary IH in a 4-month-old infant [10]. At the World Congress of Paediatric Dermatology in Bangkok in 2009, Pope and Chakkiakan-diyil [11] reported on a pilot study showing that topical timolol had successful effect in the treatment of superficial IH. Timolol does not penetrate deeply and can be only used in superficial IH. The mechanism of action is not clear, but presumably is the same as for propranolol [6]. The advantages of topical timolol are low cost, ease of administration, and minimal risk of drug-related adverse events. Several case reports connect wheezing, bradycardia, and respiratory depression, especially in infants with the long-term use of timolol ocular solution [3]. Also several cases of contact allergy to timolol and related drugs have been described [6]. No side effects were observed in our patient. After three-month treatment the result was excellent, and response to timolol treatment was stable over time. Ophthalmic timolol gel has been shown to have less or insignificant systemic bioavailability than timolol ophthalmic solution [3]. Small residual IH in the facial area are not an indication for treatment, but in our case were the source of parents concern. We think, that in the case of any visible abnormalities in the facial area, as far as IH are concerned, there is a certain necessity for treatment.

Conclusion

Timolol gel is an effective therapy option for residual hemangiomas, and should be considered as a complementary

treatment for residual hemangiomas after terminating propranolol treatment.

Authors' contribution/Wkład autorów

EM – study design, data collection and interpretation, literature search. MO – study design, data collection. WD – acceptance of final manuscript version. ED-K, AH – study design.

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Conflict of interest/Konflikt interesu

None declared.

Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

The own research were conducted according to the Good Clinical Practice guidelines and accepted by local Bioethics Committee, all patients agreed in writing to participation and these researches.

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