Treatment of problematic infantile hemangiomas with propranolol: a series of 40 cases and review of the literature

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Summary

Infantile hemangiomas (IH) are neoplastic proliferations of endothelial cells which occur with an incidence of 10 to 12% within the first year of life. IH grow after birth and usually regress spontaneously, but still can lead to deformities when they are located in the facial areas of the lip, eyelid, nasal tip or the ear. We wanted to share our experience in the treatment of problematic IH with propranolol. A retrospective review of medical charts was performed for 40 consecutive children treated with propranolol because of problematic IH between 2009 and 2012. 40 patients (33 girls, 7 boys) with a median age of 4.2 months (aged 1 to 11 months) were treated because of problematic IH. Rapid improvement was reported in the first days of treatment in 38 patients. In one case we had to terminate the treatment because serious tachycardia developed within the first 48 hours after propranolol was started. In this case the patient benefited from alternative treatment with timolol maleate gel. 35 patients (87%) showed an excellent response with complete resolution of the lesion. 4 patients (10%) showed a good result with >50% reduction in the size of the hemangioma. Also a patient with residual IH after terminating oral propranolol benefitted from topical treatment with timolol maleate gel. A minor side effect was poor weight gain during prolonged treatment in one patient and tachycardia in another patient in which case we had to terminate the treatment. Conclusions: Our observations show that gradually increasing the dosage of propranolol up to 3 mg/kg and gradually weaning the dosage is safe and effective in treatment of problematic IH. Timolol maleate gel should be considered as a complementary treatment for residual hemangiomas after terminating propranolol treatment or as an alternative treatment in patients who do not tolerate oral propranolol well.

Key words: hemangioma • children • timolol • propranolol • residual hemangioma
Introduction

Infantile hemangiomas (IH) are neoplastic proliferations of endothelial cells, which grow after birth and usually regress spontaneously [20]. IH 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 IH than male infants [8]. 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. The majority of IH can be left untreated and allowed to follow their natural course. However, a significant proportion of hemangiomas are associated with substantial morbidity in infancy and childhood [8]. IH can be life-threatening when present in the upper airways, brain and liver, by inducing acute respiratory failure and congestive heart failure respectively [8,20]. IH also can lead to deformities when they are located in the facial areas of the lip, nasal tip or the ear. It is difficult to assess whether IH will continue growing or regress spontaneously. There are often residual findings [8,20]. Although the majority of residual IH are esthetically insignificant, in visible locations they may still be the cause of parents’ concern. The treatment of even small hemangiomas 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 [8,20]. Corticosteroids and propranolol may both have significant systemic adverse effects [3,24]. A limited number of topical agents have been adapted for treatment of IH – corticosteroids and imiquimod [18]. Small IH were also treated by pulse dye laser (PDL) [18]. Recently, timolol maleate gel, a topical nonselective beta-blocker, has been reported as a potential new topical agent for superficial IH [22].

Methods

A retrospective review of medical charts of consecutive patients with problematic IH treated with propranolol in the Pediatric Surgery Department was performed. 40 patients (33 girls – 82%, 7 boys – 8%) aged from 1 to 11 months (mean 4.2+/−6 days) were hospitalized because of problematic IH. The location of the IH varied as follows: n=20 in the head and neck area (50%), n=13 on the chest (32%), n=4 on the extremities (10%), and n=3 on the genitalia (8%) (Fig. 1, 2). Problematic IH was defined as any lesion that was rapidly progressive, or ulcerating or recurrently bleeding, or compromising vision, feeding, micturition or defecation. Also IH was located in the facial area, which most likely would lead to a cosmetic deformity in the future (Fig. 1, 2). In every patient a thorough physical examination was performed before the start of the therapy in order to exclude infections and rule out treatment contraindications. All patients were also subjected to a detailed cardiac evaluation: echocardiography and ECG were performed and blood pressure was taken. With the written consent of parents propranolol was commenced at the dosage of 1 mg/kg in equally divided doses. Fractionation and gradual increase in the dosage is crucial as the safety of propranolol on cardiac rhythm and rate has always been a concern.

The improvement of IH was defined as a change in the hemangioma color from intense red to a lighter shade. Complete resolution of IH was defined as no color spots left in the location of IH. Partial resolution of IH was defined as residual red color spots in the location of IH.

Results

Patients were kept under observation for the first 72 h. Potassium, sodium, chloride, glucose, liver enzymes, blood count, blood pressure, heart rate and ECG were monitored. During three consecutive days the dosage of propranolol was gradually increased to 3 mg/kg and if observations were stable, patients were discharged home. All patients had scheduled their follow-up visits every month, and were subjected to full clinical evaluation and photographic documentation. ECG and laboratory investigations were performed. All patients had baseline resting heart rates normal for their age within a range of 92-120 BPM parameters. All patients had systolic and diastolic blood pressure between the 10th and 75th percentiles for age. Echocardiographic assessments were normal in all patients. Upon follow-up none of the assessed parameters (heart rate, blood pressure and ECG) showed any statistically significant differences as compared to baseline parameters. Side effects associated with propranolol treatment were recorded, as well as relapses after treatment cessation. Treatment was gradually terminated (dosage reduced to 2 mg/kg for one month and 1 mg/kg for the last month of therapy) if complete resolution of IH occurred, if any intolerable side effects from propranolol developed, or if residual IH was stable over a period of 2 months treatment.

The initial response was reported within the first 72 h of treatment in 38 patients (95%). The improvement was the change in the hemangioma color from intense red to a lighter shade, associated with palpable softening of the lesion. In 39 patients the propranolol treatment was continued for a duration of 1.5-17 months (mean duration 6 months ± 16 days). 35 patients (87%) showed an excellent response with complete resolution of the lesion. 4 patients (10%) showed a good result with >50% reduction in the size of the hemangioma (Fig. 3, 4). Also 2 cases of ulcerating IH showed successful heal-
Wprowadzenie

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AP-1 – czynnik transkrypcyjny AP-1; APC – komórka prezentująca antygen (antigen presenting cell); CD – kompleks różnicowania (cluster of differentiation); CDR – region

ing within 1 month. We had to stop the treatment in one 3-month-old girl because serious tachycardia (160 BPM, sinus rhythm) developed during the first 72 h of commencing propranolol. In one girl poor weight gain during prolonged treatment was noted. During ambulatory treatment we did not observe other adverse effects such as hypotension, bradycardia, hypoglycemia and bronchospasm. Of the 39 patients who showed a response to the propranolol therapy, 2 patients aged 12 and 13 months showed evidence of rebound growth during gradual reduction of the dosage. This occurred as a sudden increase in size and worsening of the color. In these girls again the dose was increased to 3 mg/kg. At the age of 1 year the dosage was reduced and the treatment was gradually terminated. The girl who developed severe tachycardia during commencing propranolol received alternative treatment with timolol maleate gel with a good result. Also 4 patients with residual IH after terminating oral propranolol benefited from topical treatment with timolol maleate gel (Fig. 5). Timolol 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. No side effects were reported by the parents. After three-month treatment the result was excellent – the lesion resolved completely. The response to timolol treatment was stable over time.
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 [16]. In most case reports, propranolol was not used as a single therapy of IH; patients received concomitant systemic or intralesional steroids and laser treatment [19]. 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 [25].

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 in-
duction of apoptosis [25]. Treatment with propranolol may cause severe systemic complications and infants need to be closely monitored [3,8,16,18,19,20,22,24,25]. During propranolol therapy of our patients, potassium, sodium, chloride, glucose, liver enzymes, blood count, vital signs and ECG were monitored. The most common reported side effects of propranolol include hypotension, bradycardia, hypoglycemia and bronchospasm [8,16,18,19,20,25]. 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 [20]. During ambulatory surveillance we did not observe hypoglycemia, hypotension or other adverse cardiac effects. The treatment was well tolerated. Despite the high dosage of propranolol (3 mg/kg/day) the only side effect in our patients was poor weight gain during prolonged treatment. We had to stop the treatment in only one patient because of severe tachycardia that developed during the first 72 h after commencing propranolol. There is no accepted consensus on the treatment regime with propranolol, but our observation enforces the belief that gradual increase of the dosage of propranolol up to 3 mg/kg and gradual weaning of the dosage is safe and effective in treatment of IH. Still, a full cardiovascular work-up should be performed prior to the initiation of propranolol therapy, to identify patients in whom the commencement of propranolol therapy could be dangerous [13,17].

Despite the great efficacy of propranolol, relapses may occur. Among our patients two girls showed evidence of rebound growth during reduction of the dosage. This observation is supported by other studies [13,17]. This can be explained by the fact that in the first year IH is in the active proliferative phase which gradually comes to an end with the change of the balance between pro-angiogenic and pro-apoptotic factors [2]. Bearing in mind these observations, we think that therapy should be prolonged beyond 12-18 months of age.

Vascular tumors can have life-threatening complications including severe thrombocytopenia as part of Kasabach-Merritt syndrome (KMS) [3,8,16,20,24]. Vascular tumor associated with thrombocytopenia in an infant (KMS) was first described by Kasabach and Merritt in 1940 [14]. KMS occurs in approximately 0.3% of infants with vascular tumors and is quite rarely associated with infantile hemangiomas, in most cases associated with kaposiform hemangiofibroma or tufted angiomas. Mortality rates of 10-37% have been reported resulting from hemorrhage, infection, invasion of vital structures, and multiple organ failure [3,8,16,18,20,24]. The goal of treating KMS associated with vascular tumor is to control the thrombocyto-
penia and avoid lethal complications. Currently, there are no known treatment guidelines for KMS [12]. Several multimodality regimens have been described but with variable success and many side effects. Pharmacological treatments include systemic corticosteroid therapy, interferon therapy, anti-cancer drugs, and anti-platelet therapy. Supportive therapies include FFP and platelet transfusions. Patients with high-output cardiac failure need management to avoid further cardiac compromise [3,8,12,18,20,24].

High-dose prednisolone (2 mg/kg/day) therapy was reported to be successful in some cases of KMS, but was ineffective in other reported cases [6]. Corticosteroids have antiangiogenic properties, and facilitate intravascular thrombosis by inhibiting fibrinolysis. Nonetheless, it is not unusual that hemangiomas increase in size after steroids are withdrawn, so that multiple courses of therapy are necessary. In contrast to the excellent steroid response rate for skin hemangiomas (90%), a similar result has not been reported for KMS (30-50%) [12,15]. Side effects associated with steroid treatment include hypertension, cushingoid appearance, growth suppression and opportunistic infections [15]. Interferon alpha2b therapy remains controversial, with a response rate of about 50% [7,26]. The adverse effects of interferon therapy include flu-like symptoms, neutropenia, and spastic diplegia in infancy [26]. Vincristine is another treatment option, and there are reports of increased platelet count and a significant decrease in the vascular tumor size in patients treated with vincristine, but complications included abdominal pain, irritability, and transient loss of deep tendon reflexes [10]. Heparin and anti-platelet therapy have been reported to have varied success [6]. Surgical resection can be the definitive treatment for KMS, but in most cases it is not possible because of the location and size of the vascular tumor; the patient must be hematologically stable [4,6]. Another option is transarterial embolization, and successful treatment of KMS with embolization has been reported with several embolic materials, such as coils, PVA, and onyx [6]. A large review of 153 reported cases in 33 published articles undertaken by El-Dessouky showed that the combination of radiation therapy with corticosteroid therapy produced the best results in the treatment of KMS and was superior to surgery or corticosteroid therapy alone [5]. The mechanism of action of radiotherapy may be related to inhibition of cellular proliferation in vascular endothelial cells. The main problem with the use of radiotherapy for KMS is the risk of late effects and carcinogenesis. In Mitsushita’s series, three patients who received multiple courses of radiation were left with shortening of the involved extremity [21]. A total of 248 malignancies were recorded in the Swedish Cancer registry up to 1989, in infants with IH (n=11 807) treated with brachytherapy between 1930 and 1965 [26]. Although propranolol now is widely used for the treatment of IH, apart from two articles there are no detailed data in the literature regarding treatment of KMS associated with vascular tumors with propranolol [11]. In cases reported by Arunachalam propranolol treatment was combined with steroids, while in the case reported by Hermans propranolol was combined with vincristine and radiotherapy. Supportive therapies include FFP and platelet transfusions. Patients with high-output cardiac failure need management to avoid further cardiac compromise [3,8,12,18,20,24].
Several studies have reported that topical timolol gel is effective and safe for the treatment of IH and can be an alternative or complement systemic propranolol [9]. Topical timolol is effective not only in stopping hemangioma growth, but also in decreasing tumor volume [9].

Guo and Ni were the first to report the positive effects of the use of topical timolol in treating capillary IH in a 4-month-old infant [9]. At the World Congress of Pediatric Dermatology in Bangkok in 2009, Pope and Chakkittakandiyil reported on a pilot study showing that topical timolol had a successful effect in the treatment of superficial IH [23]. Timolol does not penetrate deeply and can only be used in superficial IH. The mechanism of action is not clear, but presumably is the same as for propranolol [22]. 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 [22]. No side effects were observed in our patient. After three-month treatment the result was excellent, and the 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 cases 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.

**Conclusions**

Our observations support the view that gradually increasing the dosage of propranolol up to 3 mg/kg and gradually weaning the dosage is safe and effective in treatment of problematic IH. A minor side effect was poor weight gain during prolonged treatment in one patient and tachycardia in other patient, in which case we had to terminate the treatment. Timolol maleate gel should be considered as a complementary treatment for residual hemangiomas after terminating propranolol treatment or as an alternative treatment.

**References**


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The authors have no potential conflicts of interest to declare.