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# β-blockers in the treatment of periocular infantile capillary haemangioma

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Infantile capillary haemangioma (IH) is the most common congenital vascular tumor of childhood and infancy. Although the majority of these lesions regress spontaneously, many of children with IH particularly in the periocular or orbital region need treatment. Ocular indications for treatment include obstruction of the visual axis or high degrees of astigmatism causing amblyopia, exposure keratopathy secondary to proptosis or compressive optic neuropathy. Our purpose was to assess the effectiveness and tolerance of beta-blockers (BB), propranolol and metoprolol, in the treatment of these lesions. We performed a retrospective review of 21 infant patients with periocular or/and orbital IH. The mode of treatment for 13 patients was with the non-selective β blocker propranolol (PR) and 8 patients were treated with the β1 selective blocker metoprolol (ME). We analysed the changes in IH lesion size, colour and thickness after the treatment with β-blockers, the onset and the period of their action, recurrence of IH and adverse effects of the treatment. The effectiveness of metoprolol to propranolol was compared as well as their use in combination with systemic steroids. In the first month of the treatment with beta-blockers, significant regression of the IH was observed in all patients. During the following months of treatment the regression was not rapid and after 6 to 12 months the lesions remained stationary. The final result of the treatment of 15 patients (71.4%) was deemed excellent while the treatment of 5 patients (23.8%) was deemed good. A single patient (4.7%) had only fair response to the therapy. During the whole series no serious life-threatening adverse effects were observed. The usage of beta-blockers, both propranolol and metoprolol, in the therapy of orbital and periocular capillary infantile haemangioma seems to be very effective in reduction of the tumor and had only rare, minimum adverse effects. These facts favour beta-blockers as the first line treatment of children with IH.

*Key words: Infantile capillary haemangioma, periocular, beta-blockers, metoprolol, propranolol*

Capillary haemangioma is the most common congenital vascular tumor of childhood and infancy affecting approximately 10% of all infants (1, 2). They are benign endothelial cell neoplasms that are typically absent at birth (70%) but characteristically have rapid growth in the following weeks and months of infancy. About 80% of haemangiomas are located in the head and neck regions (3). Classification of these lesions is based on the level of involvement: superficial, subcutaneous, deep orbital, or combined (4).

Periorbital capillary haemangiomas follow a similar course to haemangiomas on other parts of the body. They have two phases of growth, a proliferative phase and an involution phase. The proliferative phase of rapid growth (usually achieved within the first three months of age) is characterized by an increased number of endothelial mast cells and vessel growth. The involution phase is characterized by slow regression of the haemangiomas. Although the natural history of an IH is spontaneous regression during the first decade of life, a high proportion of children with periocular IH will need treatment (5). Ocular indications for treatment include obstruction of the visual axis by the haemangioma or high degrees of astigmatism causing amblyopia, exposure keratopathy secondary to proptosis, compressive optic neuropathy or rarely bleeding from the lesion (6, 7). Several treatment modalities have been used in the management of haemangiomas, including intralesional or systemic steroids, surgery, embolization, radiation, interferon therapy, and laser therapy with variable efficacy and safety. (6, 8, 9, 10, 11)

In recent years the use of beta-blockers has been reported to be very effective in the treatment of IH. The non-selective beta blocker propranolol was serendipitously found to induce early involution in haemangiomas (12, 13) and is now considered as a highly promising pharmacological agent for the treatment of periocular capillary haemangiomas, especially in deep orbital

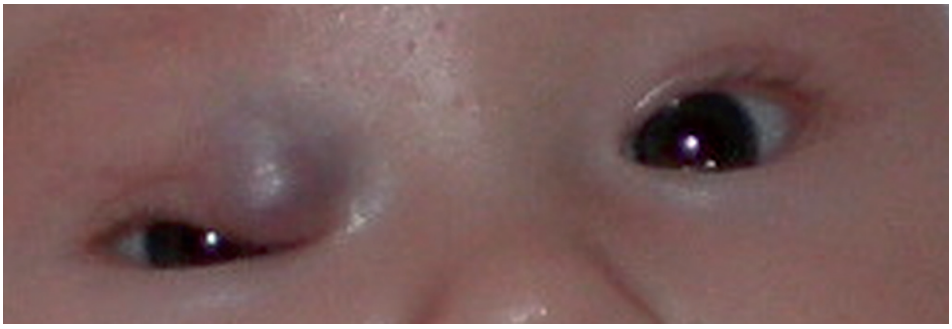

**Figure 1. Patient with IH at three months before initiation of treatment with metoprolol**

lesions. For smaller and superficial lesions, topical treatment by the beta-blocker timolol can be used.

## Patients and methods

A total of 21 patients (17 females, 4 males) with orbital or periocular IH were treated and followed at the Paediatric Ophthalmology Department in Bratislava in the period between January 2009 and June 2014. The localization of IH was upper eyelid (10 patients), lower eyelid (6 patients), and radix of the nose and surrounding area (5 patients). Therapy with BB was indicated in all patients because of the high risk of functional impairment – amblyopia, and/or cosmetic disfigurement caused by progression of IH. The median age of the appearance of IH was 0.7 months (m) (the range was from 0 to 2.4 months). The median age of the onset of the therapy with BB was 6.4m (the range was from 0.9 to 27.3m). Before treatment, all patients had been admitted (for a short time) to the Department of Paediatric Ophthalmology in Bratislava and had undergone thorough clinical examination by a paediatrician and a paediatric cardiologist. Complete ophthalmologic examination was conducted and photo documentation and ultrasonography, CT or MRI examination was performed for patients with orbital involvement (Fig. 1, 2). Then oral BB therapy was initiated in all children in a dose of 2 mg/kg per day divided in two doses. ECG, blood pressure, pulse rate and blood glucose level were monitored in the first 24-48 hours of BB therapy. The next period of the therapy and clinical monitoring was continued on an outpatient basis, first after 1 week of treatment, second after 2 weeks, then after 1 month, 2-3 months, after cessation of the therapy with BB, and then every 2.3 to 6 months. The median period of the therapy with BB was 12.1m (range from 4.3 to 34.6m). The median follow up period was 36.4m (range from 2.0 to 64.7m).

Thirteen patients (61.9%) were treated with the non-selective beta-blocker propranolol and 8 patients (38.1%) were treated with the selective β1 metoprolol in the same dosage of 2mg/kg/day. In the treatment of 13 patients (61.9%) local steroids were used and 8 patients (38.1%) were treated with a combination BB with systemic steroids (prednisone in the dosage of 2mg/kg/day for 4-8 weeks, then gradually reduced). Eight (38,1%) patients were treated only with beta-blockers. Seven patients (33.3%) were treated also with local beta-blocker 0.2% ointment, timolol, during or after the therapy with BB

The medical records of the patients were analysed retrospectively. The effectiveness of the treatment was evaluated qualitatively. Reduction of the volume and size of the IH and change of the IH colour and stiffness with palpation were taken into consideration in the assessment. According to these criteria the final result was deemed as: 1. excellent if there was striking regression of colour volume and size of the IH; 2. good if there was improvement but not as marked as in the first group; and 3. fair when there was only a mild improvement in the first weeks of the therapy and the lesion then seemed to remain stationary or there was a little progression of IH.

Adverse effects and recrudescence of IH were also analysed.

## Statistical analysis

Data were analysed using a statistical program (JMP Statistical Analysis, Cary, NC). Descriptive statistics were expressed as a median and a range. Continuous variables were analysed with Likelihood Ratio and Fisher's Exact Test.

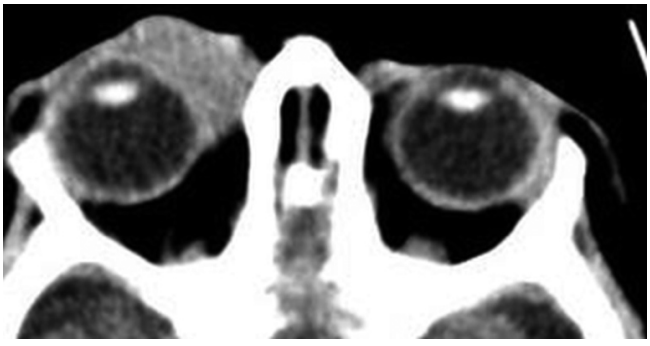

**Figure 2. CT finding before treatment**

The Kaplan-Meier method was used to determine event-free survival curves. (Subgroups were compared with the use of the log-rank test).

## Results

We evaluated and analysed data from 21 patients treated with beta-blockers. (Table 1) All 21 patients responded positively to the therapy in the first month, mostly in the first two weeks. There was rapid change of the colour and marked reduction in the volume of IH (Fig. 3). This regression was not as rapid in the next period of the therapy and after 6 to 12 months there was only mild improvement (Fig. 4, 5), the lesions remained stationary or in some patients mild progression was detected. The final result after cessation of BB therapy was deemed as excellent in 15 patients (71.4%) and as good in 5 patients (23.8%).In the latter 5 patients after some period after cessation of therapy – a median of 1.99 months (range from 0.3m to 6.1m) – mild progression or recrudescence of IH was observed. Five patients with recrudescence of IH received second line BB therapy in a dose of 2mg/kg/day in the median therapy period of 18 months. After this therapy there was partial regression of IH in all patients; in 1 patient Nd YAG laser therapy was used and surgical excision was recommended and planned for 3 patients. The final result was deemed as fair in 1 patient (4.7%). The treatment of this patient included the use of a combination with systemic steroids but there was a poor response to this therapy. This patient's diagnosis was reassessed as low flow vascular malformation as there was a positive response only during the therapy with BB and steroids and after their cessation there was rapid progression again. Surgical excision was recommended and planned for this patient. No serious life-threatening adverse effects were observed during the BB therapy; in six patients (28.5%) only a few mild adverse effects were observed: mild thrombocytosis (3 patients), mild anaemia (1 patient), granulocytopenia (1 patient), gastro-esophageal reflux and vomitus in one patient (improved after a change of diet), and mild pruritus in one patient. Three of these patients were treated also with systemic steroids and all of them had been treated with propranolol.

The topical ointment timolol was used in addition to oral administration of beta-blockers or after the systemic therapy in the treatment of seven patients. All of them benefited from this therapy.

**Table 1. Summary of Patient Characteristics and Outcomes**

| Patient | M/F | Age at appearance of IH (weeks) | Age at the onset of therapy (months) | Localization of the IH | Type of BB | Duration of the therapy (months) | Other therapy | Results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| LB | F | 3w | 8m | upper eyelid OD | metoprolol | 12 | | excellent | 0 |
| RK | F | 2w | 27m | radix of the nose | propranolol | 12 | diprophos prednisone | fair | 0 |
| BS | M | 6w | 13m | upper and lower eyelid + orbit OD | propranolol | 13 | prednisone | excellent | 0 |
| TM | F | 4w | 2.5m | radix of the nose + periocular | propranolol | 9 | | good | mild trombocytosis |
| RRM | F | 1w | 2.5m | upper eyelid OS | propranolol | 5 | | excellent | mild trombocytosis |
| OO | M | 1w | 4m | upper and lower eyelid + orbit OD | metoprolol | 14 | | excellent | 0 |
| AP | F | 2w | 3m | upper eyelid + orbit OS | propranolol | 27 | prednisone Nd YAG laser | good | Pruritus |
| TP | F | 2w | 2m | orbit | propranolol | 24 | diprophos prednisone | good | GER, vomitus |
| GS | F | 6w | 10m | lower eyelid OS | propranolol | 15 | diprophos prednisone | excellent | 0 |
| LS | F | 11w | 6m | radix of the nose | propranolol | 8 | prednisone | good | mild trombocytosis, anemia |
| KES | F | 4w | 8m | upper eyelid OS | metoprolol | 8- | | excellent | 0 |
| SŠ | F | 3w | 6m | radix of the nose | metoprolol | 5- | diprophos | excellent | 0 |
| VŠ | F | 4w | 8.5m | upper eyelid OD | metoprolol | 12 | diprophos | excellent | 0 |
| ZV | F | 1w | 12m | lower eyelid OD | propranolol | 4 | diprophos | excellent | mild granulocytopenia |
| DV | F | 2w | 9m | upper eyelid OD | metoprolol | 24 | diprophos prednisone | good | 0 |
| ANV | F | 4w | 12m | radix of the nose + orbits . | propranolol | 5 | diprophos prednisone | excellent | 0 |
| EV | F | 2w | 2m | lower exelid OD | metoprolol | 11 | diprophos | excellent | 0 |
| MV | M | 3w | 9m | lower eyelid OD | propranolol | 34 | | excellent | 0 |
| JZ | M | 4w | 5.5m | upper eyelid OS | propranolol | 12 | | excellent | 0 |
| LĎ | F | 4w | 5.5m | lower eyelid OS | metoprolol | 14 | | excellent | 0 |
| TS | F | 4w | 1m | upper eyelid OS | propranolol | 12 | diprophos | excellent | 0 |

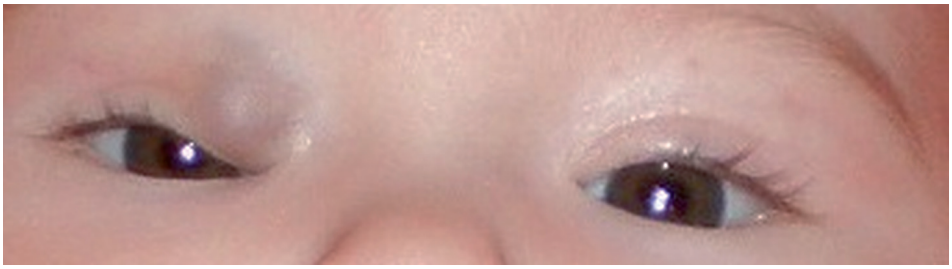

**Figure 3. The patient at seven months after 4 weeks of systemic treatment with metoprolol**

We compared the therapy with non-selective propranolol (PR) to the beta 1 selective metoprolol (ME) from the point of efficacy, adverse effects and recurrence of IH (Table 2.). Eight patients were treated with ME and seven of them (87.5%) had an excellent result. Thirteen patients were treated with PR and 8 of them (61.5%) had an excellent result. The recurrence of IH after cessation of ME therapy occurred in one patient (12.5%), after PR therapy it occurred in five patients (38.5%) and these results are interesting but statistically insignificant (p=0.2). The occurrence of mild adverse effects occurred in none of the patients with ME therapy and with six patients (46.2%) with PR therapy and that is statistically significant (p=0.023).

Steroid therapy i was used in thirteen patients (61.9%). Five patients (23,8%) received local intralesional injections and eight patients (38,1%) received the systemic steroid prednisone in combination with BB. Intralesional injections of steroids had no effect or only a mild effect. The comparison of recurrences in patients who received local or systemic steroids in combination with BB is interesting. The recurrence of IH was only in the second group (systemic steroids)and it involved five patients. All of these patients had larger, deep combined IH (Table 3).

**Table 2. The comparison of propranolol and metoprolol (effectiveness, adverse effects, recurrence)**

| | Propranolol | Metoprolol |
|---|---|---|
| The number of patients | 13 | 8 |
| Excellent result | 8 | 7 |
| Good result | 4 | 1 |
| Fair result | 1 | 0 |
| Adverse effects | 6 | 0 |
| The recurrence of IH | 5 | 1 |

## Discussion

Beta-blockers have been recently considered as a first line treatment of deep or combined orbital and periocular IH. The effectiveness of the non-selective beta blocker propranolol was

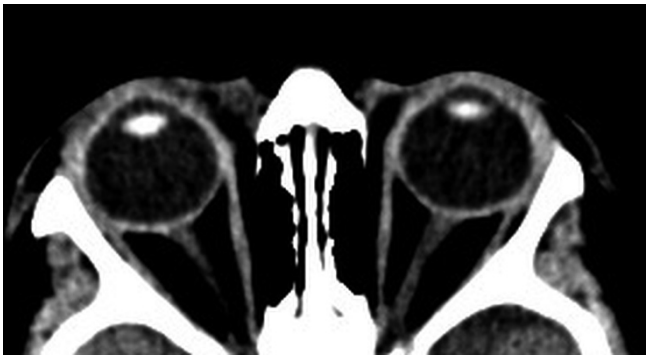

**Figure 4. CT finding of the patient at one year after 6 months of treatment with metoprolol**

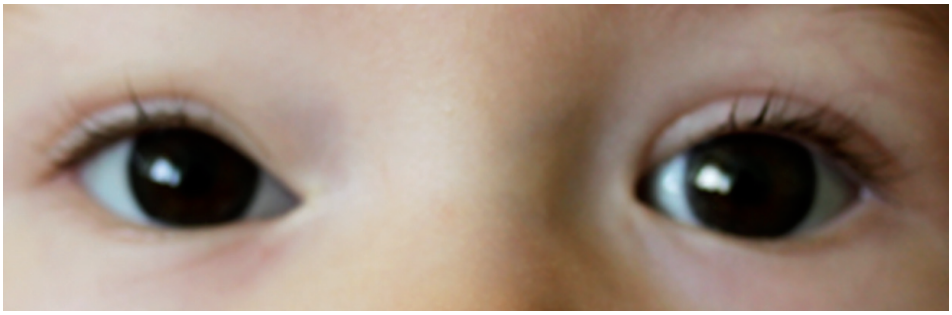

**Figure 5. The patient at 16 months after 10 months of treatment with metoprolol )**

**Table 3. The comparison of the treatment with Beta-blockers (BB) separately and BB+steroids**

| | BB | BB+local steroid | BB+systemic steroid |
|---|---|---|---|
| The number of patients | 8 | 5 | 8 (5 of them also local steroid) |
| Deep orbital or large IH | 2 | 1 | 8 |
| Recurrence of IH | 1 | 0 | 5 |

first published by Léauté-Labréze and co-workers in 2008 (12). In their study (11 patients) they found significant regression of IH (decrease in size and improvement of appearance) after treatment with propranolol (dosage of 2mg) and the authors did not report any adverse side effects. Lawley et al. were probably the first to report some adverse effects – bradycardia and hypoglycaemia after treatment with propranolol (14). According to our knowledge, the first randomized controlled trial of propranolol for IH was conducted by Hogeling and co-workers in 2011 (15). This study revealed the effectiveness and good tolerance of propranolol. Significant differences were seen in the percent change in volume, redness and elevation of IH between propranolol and the control group. Consequently, several case reports and retrospective studies were published, usually with a smaller sample of patients, which confirmed the high effectiveness of propranolol treatment for IH with few or no adverse side effects. These side effects included asymptomatic bradycardia, gastrointestinal symptoms, asymptomatic hypotension, cool hands/feet, asymptomatic hypoglycaemia and sleep disturbance (16). In our study none of the patients had any of these side effects or any other serious adverse effects; 6 patients had only mild adverse effects (gastroesophageal reflux, pruritus, mild thrombocytosis and mild anaemia). Although the effectiveness of propranolol treatment is unquestioned, in some cases there has been no response or the recurrence of IH after cessation of therapy. This has been reported in 10-13% of patients in the literature (16, 17, 18). Philips and co-workers reported that focal facial lesions failed to respond twice as frequently as other types of haemangioma. They examined the tissue sections but no histopathological reason was identified indicating why some haemangiomas failed to respond (17).

In our study there was significant regression of IH in the first period of the treatment in all patients, but recurrence of IH after cessation of therapy occurred in 5 patients (23.8%) and is higher than previously reported. In all cases these lesions were larger, deep orbital or combined and after the second line of the therapy with BB there was improvement of IH and surgical excision was recommended and planned in 3 patients.

The positive effectiveness of the non-selective beta-blocker (propranolol) has been published many times while the effectiveness of beta1 selective blockers or its comparison has been only rarely documented, especially for orbital and periocular IH. De Graaf et al (19) in their study of 30 patients reported that the effects of atenolol seemed to be similar and were less frequently associated with severe side effects. Abarzúa-Araya, Álvaro, et al. (20) in their randomized controlled study of 23 patients did not find significant differences between propranolol and atenolol in their effectiveness and adverse events in the treatment of IH. In our study we found that the effectiveness for metoprolol therapy was more favourable but not statistically significant compared to propranolol, even after the recrudescence of IH after cessation of the therapy. Interesting and statistically significant (p=0.023) is the occurrence of some mild adverse effects with 6 patients treated with propranolol compared to no patients treated with metoprolol.

Local treatment with the topical beta-blocker timolol seems to be effective for smaller superficial non-vision threatening periocular capillary IH (21). In our study, 6 of 7 patients benefited from this combination of local and systemic BB.

## Conclusion

Beta-blockers seem to be very effective in the treatment of IH in the periocular and/or orbital region at a dose of 2mg/kg/day divided in two doses. The effectiveness of the therapy is the highest in first 6 months and after this period the regression of IH is slower and after 12 months IH seems to remain stationary. Nevertheless, the duration of the treatment should be for a mean period of 12 months because of the risk of reoccurrence of IH after cessation of the therapy. Non-selective BB and beta1-selective BB appear to have similar effectiveness and beta-selective BB metoprolol appears to have even better tolerance and a lower occurrence of adverse effects than non-selective propranolol. The use of the local beta blocker timolol ointment appears to have been favourable both in combination with systemic treatment or after cessation of the systemic BB therapy when the regression of the IH was not complete.

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