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Propranolol as an effective treatment for inoperable periocular haemangiomas in children

Propranolol jako skuteczna metoda leczenia nieoperacyjnych naczyniaków okołoocznych u dzieci

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ABSTRACT

Introduction: Infantile haemangiomas located in the periocular region are a significant clinical problem. When untreated, they can lead to serious complications that can inhibit the proper development of vision. As they are often inaccessible surgically, a noninvasive eye-saving therapy is required.

The aim of the study was to assess the effectiveness of propranolol treatment for inoperable periocular haemangiomas (PH) in children.

Material and methods: Seventeen children with haemangiomas of the upper and lower eyelid and internal eyelid angle were thoroughly examined. Lesions were seriously affecting movement of eyelids leading to ptosis in most of cases, but anisometric astigmatism and exophthalmia were also diagnosed. Patients were carefully qualified for propranolol treatment and were re-evaluated when therapy was completed.

Results: In all of the described cases brightening and softening of the lesion were observed from the first days of therapy. Ninety percent of patients showed signs of complete involution. In 5 cases a mild discolouration or skin enhancement persisted. All children presented significant functional improvement. An 86% reduction of astigmatism was found in cases that were diagnosed initially.

Conclusions: In conclusion, early diagnosis and introduction of propranolol for PH reduce the risk of complications that pose a threat to eye function. Measurement of astigmatism reduction may be a useful tool to establish a proper moment to cease the therapy. Propranolol is the first choice treatment option in PH based on its effectiveness, speed of action, and low rate of side effects.

Keywords: infantile haemangioma, periocular haemangioma, astigmatism, propranolol.

STRESZCZENIE

Wstęp: Naczyniaki wczesnodziecięce w lokalizacji okołoocznej to poważny problem kliniczny. Nieleczone mogą prowadzić do poważnych konsekwencji, stwarzając zagrożenie dla prawidłowego rozwoju wzroku. Z uwagi na trudną lokalizację bywają nieoperacyjne, dlatego niezbędne jest małoinwazyjne leczenie oszczędzające oko.

Celem pracy była ocena skuteczności leczenia propranololem nieoperacyjnych naczyniaków okolicy oczodołu u dzieci.

Materiał i metody: Do badania włączono 17 dzieci z naczyniakami górnej i dolnej powieki oraz kąta wewnętrznego powiek. Pacjentów poddano szczegółowemu badaniu okulistycznemu. Guzy naczyniowe znacząco wpływały na prawidłowy ruch powiek, powodując w większości przypadków opadanie powieki. Ponadto zdiagnozowano przypadki astygmatyzmu anizometrycznego oraz wytrzeszcz. Pacjenci zostali zakwalifikowani do terapii propranololem i szczegółowo ocenieni po zakończeniu leczenia.

Wyniki: We wszystkich opisanych przypadkach od pierwszych dni stosowania leku zaobserwowano rozjaśnienie powierzchni guza oraz zmniejszenie jego napięcia. U 90% pacjentów doszło do całkowitej inwolucji. W 5 przypadkach pozostało delikatne przebarwienie i zgrubienie skóry. U wszystkich dzieci doszło do znaczącej poprawy w zakresie funkcji narządu wzroku. Stwierdzono 86% redukcję astygmatyzmu w przypadkach, gdy był on zdiagnozowany wyjściowo.

Wnioski: Wczesna diagnoza i szybkie włączenie propranololu w leczeniu naczyniaków okolicy oczodołu u dzieci obniża ryzyko powikłań zagrażających prawidłowemu widzeniu. Pomiar redukcji astygmatyzmu może być przydatny w monitorowaniu terapii. Propranolol jest lekiem z wyboru w przypadku naczyniaków okołoocznych, uwzględniając jego skuteczność, szybkość działania i mały odsetek występowania objawów ubocznych.

Słowa kluczowe: naczyniak wczesnodziecięcy, naczyniak okołooczny, astygmatyzm, propranolol.

INTRODUCTION

Infantile haemangioma (IH) is the most common benign tumour of infancy [1, 2, 3]. Periocular haemangiomas (PH) are a significant problem [4, 5, 6]. A rapid growth of the lesion can cause ptosis leading to amblyopia. Displacement of the globe increases the risk of strabismus. Mechanical deformation of the immature sclera and cornea can cause anisometric astigmatism and refractive amblyopia. The severe complications are disfiguring proptosis, compressive optic neuropathy, as well as facial and eyelid deformation [4, 7]. Propranolol is a pharmacological treatment for threatening life function haemangiomas of still unclear mechanism of action [8, 9, 10].

The goal of the study was to assess the effectiveness of propranolol treatment for inoperable periocular haemangiomas in children.

MATERIAL AND METHODS

From 2011 to 2014 at our Department 59 children were treated with propranolol for IH of various locations. This study presents an analysis of 17 patients with periocular lesions. The study complied with guidelines from a local bioethical committee, and the legal guardians of the patients agreed to the proposed pharmacological treatment and the publishing of the results and photographs.

Clinical intervention included:

1. Collecting information on the medical problem from parents, with an emphasis on the natural history of the lesion. Before, during and after the treatment was completed, the following measurements were conducted.
2. Clinical examination (for location, size, colour and consistency) with the use of the Haemangioma Activity Score (HAS) when the lesion was visible externally (Tab. 1) [2].

TABLE 1. Haemangioma Activity Score (HAS)

Deep swelling: Tense IH (6) 'Neutral' IH at t = 0 or less than 50% reduction at follow up (4) ≥50% reduction at follow up (2) No more swelling at follow up (0)
Bright red/shining red IH (5) or Bright red edge (4)
Matt red/reddish-purple IH/met red edge (3)
Blue IH or blue shining through in deep IH (2)
Grey IH (1)
Skin colored after activity (0)
Total score
Number of items scored
Preliminary HAS = total score/number of items scored
Ulcer ≤1 cm² (+0,5) Ulcer 1–25 cm² (+1) Ulcer ≥25 cm² (+2)
HAS = preliminary HAS + ulcer score

Number of points for each item is in brackets.
IH – infantile hemangioma
Source: Janmohamed et al. [2]

3. Digital photographic documentation.
4. Doppler ultrasound of the lesion.
5. Cardiologic examination with electrocardiography and echocardiography.
6. Laboratory blood tests: blood count, blood electrolytes, glucose level, AST, ALT.
7. Ophthalmic examination included: measurement of the size of the lesion and the affected orbit area (assessment of eyelid deformation, degree of ptosis); the position of eyes and their mobility; convergence reflex, straight fixation (Hirschberg test, covertest); intraocular pressure with non-contact tonometry; fundus examination (direct ophthalmoscopy); examination of the anterior eye segment using manual slit lamp and refraction evaluation (after cycloplegia with tropicamidum).
8. Administration of 2 divided doses per day of oral propranolol was planned according to the following algorithm:
   - first day: 0.5 mg/kg/day,
   - second day: 1 mg/kg/day,
   - third day: 1.5 mg/kg/day,
   - fourth day: 2.0mg/kg/day.

The first 4 to 5 days of treatment were monitored during a full-time stay at hospital with the monitoring of vital functions. This was followed by check-up visits at the outpatient clinic.

RESULTS

The analysed group consisted of 13 (76%) females and 4 (24%) males. The age at the beginning of treatment varied from 5 weeks to 21 months (mean 3 months for children under the 1st year of life). The treatment was started in a 4-year-old boy with a haemangioma of the lower eyelid, but it was ceased after 2 months due to lack of a therapeutic effect. He was not included in further analysis. Twenty three procent of patients were born pre-term with low birth weight (1700–2100 g). One was from a twin pregnancy. The mother of one of the described children had a placental anomaly diagnosed.

Lesions were examined in the upper eyelid in 7 patients, lower eyelid in 4, both in 1 (spread on the forehead, temporal and zygomatic area and upper lip), internal eyelid angle in 2, and base of nose with internal eyelid angle in 3 children. In one case, besides a haemangioma of the lower lid, a vascular malformation of the earlobe was found.

Ophthalmic examination before introducing treatment showed ptosis in 8 cases with a lesion of the upper eyelid. It was complete in 2 patients, of a high degree (4–5 mm) in 3 cases, and mild (up to 3 mm) in 3 children. Haemangiomas of the lower eyelid were diagnosed in 5 patients, affected the closure of the eyelid in 1 case, and were visible from the conjunctivas side in 3 patients. Anisometric astigmatism (difference of 1.75 DC) was seen in 2 cases, a mild elevation of intraocular pressure (2 mmHg) in 2 patients, with normal results in the rest of the children. Two PH penetrating to the orbit led to slight limitation of the eye movement in 1 case and eccentric fixation in one other. Fundus examination as well as eye globe ultrasound did not reveal any pathological changes in the eye anatomy in any of the cases.

Doppler ultrasound confirmed increased blood flow in all patients. In 2 cases magnetic resonance imaging (MRI) was conducted to precisely show the penetration to the orbit. In 1 case it had to be followed with computed tomography to exclude a malignant growth.

Time of treatment varied from 6 to 21 months (mean 12 months). It was completed in 11 children, with follow-up from 2 months to 1 year. Five other patients are in their fifth month of treatment.

The clinical examination after propranolol treatment presented a complete involution in 90% of patients according to HAS (zero points – no lesion visible or mild discoloration or skin enhancement, not regarding lesions visible only from the conjuctival side) – Table 2. One patient had a mild cosmetic effect with good functional improvement in moving of the eyelid (Fig. 1). Five patients that are still in therapy show clear signs of involution (Fig. 2). In all of the described cases brightening and softening of the lesion were observed from the first days of therapy.

TABLE 2. Haemangioma Activity Score (HAS) of one of the patients with a lesion of the upper left lid before, during and after propranolol therapy

Time	Admission	5 days	10 days	1 month	2 months
HAS	**4,3**	**3,6**	**3,0**	**2,5**	**1,5**
Time	2 months	4 months	6 month	12 months end of therapy	14 months follow-up
HAS	**1,5**	**1,33**	**1,0**	**0**	**0**

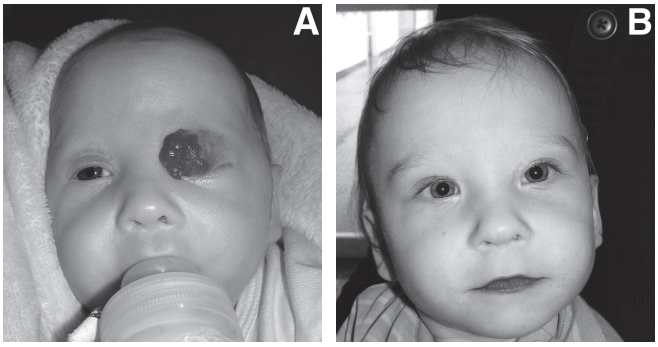

FIGURE 1. Patient with haemangioma of the left upper eyelid causing severe ptosis: A) 2-month-old child at admission – Haemangioma Activity Score (HAS) 4.3; B) after 12 months of propranolol treatment – HAS 0

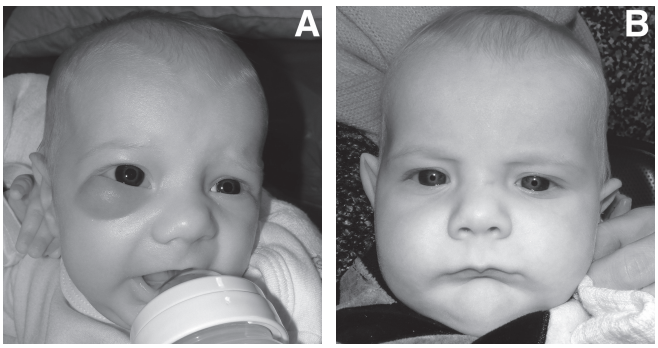

FIGURE 2. Patient with haemangioma of the right lower eyelid suspected to be a neoplasm: A) 2- month-old child at admission; B) after 100 days of propranolol, still in therapy

Follow-up ultrasound examinations after the treatment showed lowering of lesions' blood flow, with a complete disappearance in the 4–12 months of therapy in 8 cases. Another 3 children showed increased blood flow during the whole observation, with no visible clinical signs of lesion in 2 cases. Five currently treated patients showed a decrease in the size of the lesion reflected in ultrasound findings.

Ophthalmic examination showed equalization of the intraocular pressure in both eyes with a reduction of astigmatism of the eye with haemangioma compared to healthy ones of up to 0.25 DC (86%). In 2 cases where treatment was introduced after the 1st year of life, the therapeutic effects were worse, e.g. persistent constriction of the palpebral fissure. In 1 of those patients 6 months of successful treatment led to a complete involution. After it was ceased a recurrence was observed, so the child went back on propranolol. In the other case the eyelid stayed asymmetrical but propranolol enabled proper vision.

Propranolol treatment was ceased among 1.5–3 months, gradually lowering the dose and observing the lesion. No progression was seen during this period. As mentioned before, there was only 1 case of recurrence after the treatment was completed.

The following side effects were observed in the analysed group (number of patients in brackets): episodes of hypoglycaemia (1), sleep disorders (1), recurrent respiratory tract infections (1), and bradycardia (1).

DISCUSSION

The mechanism behind the development of IH is unclear. There are several theories that explain their pathogenesis. The three most common are: tissue hypoxia, embolisation of placental endothelial cells, and increased angiogenic and vasculogenic activity. Some authors have proved a correlation between the incidence of IH and placental hypoxia, low birth weight and prematurity, as they affect up to 30% of premature babies [3, 11]. In the presented material 23% of patients were born prematurely with birth weight between 1700–2100 g. One of them was from a twin pregnancy, potentially at higher risk of preterm labour, which is also one of risk factors for IH. We had a case of the coexistence of placental pathology with a haemangioma of the foetus in our material. This could be supported with a theory that treats haemangiomas as distant "metastasis" of placental cells that later lead to embolisation of small vessels, followed by hypoxia and fast proliferation. Moreover, the glucose transporter molecule 1 (GLUT-1) marker is present both in IH and placenta [11]. There is a higher incidence of haemangioma in children that undergo invasive diagnostic measures intra-utero. None of the presented theories explains the 3–5 times higher incidence in females [1]. In our group IH was present 3-times more often in girls.

Schwartz et al. showed that when PH in children is bigger that 1 centimetre at the greatest diameter there is a high risk of developing amblyopia before the third year of life [12]. It threatens 43% to 60% of children with astigmatism caused

by PH without treatment [7, 13, 14, 15]. In our study the average age when the therapy was introduced was 3 months for children under the age of 1 year, i.e. the most important time in vision development. In other publications the average age of the introduction of propranolol was slightly higher – 4 to 6 months [4, 13, 16].

All patients were hospitalized for 4 to 5 days when the pharmacotherapy was introduced with the gradual increase of the dose of propranolol. There are centres that offer such therapy in outpatient clinics [17]. Some authors suggest starting the therapy with a planned treatment dose from day 1, but the majority recommend a gradual increase of the dose [4, 13, 17]. There are various dosing algorithms. Some support lower doses as sufficient [18]. Our results prove the significant effectiveness of 2 mg/kg divided into 2 doses per day.

Children with segmental haemangiomas should be diagnosed to rule out a rare condition called "Posterior fossa malformations–Hemangiomas–Arterial anomalies–Cardiac defects–Eye abnormalities–Sternal cleft and Supraumbilical raphe syndrome" (PHACES). If such condition is diagnosed, propranolol therapy could cause a stroke due to a constriction of vessels in the posterior cranial fossa [19]. Pharmacotherapy should be carefully considered regarding possible risks and benefits. There are reports of good therapeutic effects [17]. We proceeded with diagnostic imaging measures in one unclear case, and PHACES was ruled out.

Storch and Hoeger distinguish 3 possible mechanisms of action of propranolol [9]. The early effects, such as brightening and softening of the lesion seen in the first 3 days of therapy, are explained by vasoconstriction and lower release of nitric oxide. Inhibition of the growth of the tumour is qualified as the intermediate effect. It is most likely linked with a blockage of angiogenic growth factors such as: vascular endothelial growth factor, basic fibroblast growth factor and metalloproteinase 2/9. The long-term effect – regression caused by cell apoptosis, is explained by antagonistic action against the GLUT-1 receptor, which is a specific marker, which enables the differentiation of haemangiomas from other vascular malformations [10].

The immediate effect of propranolol action on IH is fast and can be seen from the first days of therapy [3, 4, 8, 16, 17, 20]. Nonselective beta blockers lead to apoptosis of endothelial cells, which prevents recurrence [3]. Fay et al. observed a complete reduction of the lesion penetrating into the orbit causing MRI-confirmed exophtalmia within 3 months of treatment [21]. Haider et al. observed very good response in 59% of patients (mass reduction >50%), good in 35% (<50% reduction of lesion) and moderate in 6% (lack of reduction), but complete involution was observed in only 1 case [17]. There are also reports of a complete involution in all cases [16, 22]. The presented study showed lack of vessel flow in Doppler ultrasound in 72% and significant decrease in 27% of children that completed treatment. Therefore, in 90% of cases there was a complete reduction measured by HAS regarding photographic documentation. Haemangioma Activity Score is useful in monitoring the speed of reduction [2].

Astigmatism is the most serious complication of PH that can cause amblyopia. It is a clear indication for immediate treatment. Robb were the first to report high incidence (43%) of anisometric astigmatism among children with large PH [23]. In a study that comprised 81 patients with PH Ranchod et al. noted refraction disorders in 25 of them (30%) [24]. Claerhout et al. observed reduction of astigmatism from 3.8 DC to 2.25 DC in 80% of patients on propranolol; Sans et al. in all treated cases [3, 22]. In our group astigmatism was diagnosed in 2 (12%) patients, and propranolol led to its reduction from 1.75 DC to 0.25 DC (86%). Similar results were reported by Thoumazet et al. and Vassallo et al. [16, 25], while other authors noticed a 47–62% reduction [4, 13, 26]. Before propranolol was introduced, steroid injections therapy was widely applied. However, it reduced astigmatism only up to 63% under the 1st year of life and had poor effects in older children. It often caused serious complication including tissue necrosis, vessel closure and general side effects [13, 16].

Reduction of astigmatism in children prevents amblyopia and anisometropia in future life [7].

The mean length of therapy varies from 4 to 8 months [8, 16, 21, 25, 26]. In our group it was 12 months as children were younger at admission, and our decision was to continue treatment up to the first year of life. In our protocol the ceasing of propranolol was gradual, from one to 3 months, as well as long follow-up to 18 months of life to monitor the lesion until the end of the proliferative phase.

In some reports no recurrences have been noted [16, 21, 25, 27]. One of our patients was observed with a re-growth of the lesion. Probably, the treatment was ceased too early, when a complete involution was obtained as the patient was younger than 1 year. Unfortunately, due to lack of parents' consent propranolol was reintroduced with a significant delay after 18 month of life and there was no full therapeutic effect. Claerhont et al. strongly emphasize that therapy after the first year of life has a much worse potential outcome and does not lead to a complete involution [3].

Among the reported side effects of propranolol therapy, the most common is hypoglycaemia. Drolet et al. estimated its incidence in up to 0.9% of cases [19]. The exact mechanism of its development has not yet been established, but it is most likely caused by inhibition of glycogenolysis, gluconeogenesis and lipolysis. Propranolol combined with steroid therapy makes the risk of hypoglycaemia even higher. Premature babies are especially predisposed, which correlates with our patient with hypoglycaemia born in the 34th week of gestation with low birth weight. There are published cases of hypoglycaemic episodes at various stages of propranolol treatment and patients of different age. This is explained by prolonged fasting or coexisting infections [19]. The risk is the highest in the neonatal period, and therefore therapy is not recommended at that time and should be carefully considered up to the third month of life [28].

Other side effects are gastroesophageal reflux (0.7%), bradycardia (0.9%), upper respiratory tract infections (1.4%), and sleep disorders (3.7%) [19]. We observed similar results in our group. Propranolol as a nonselective inhibitor

of beta-adrenergic receptors causes bronchial contraction in children with a history of allergies. Moreover, it easily reaches the central nervous system and is responsible for irritability and nightmares in some cases. In none of our cases did we cease the therapy due to side effects.

CONCLUSIONS

1. Early diagnosis and propranolol treatment for PH in children significantly lowered the risk of complications that pose a threat to eye function.
2. Consecutive measurements of astigmatism reduction may be useful in establishing the moment to cease the therapy.
3. Propranolol is the first choice therapy for PH in children due to its effectiveness, speed of action and low rate of side effects.

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