CASE REPORT

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Cantonal Hospital Bihac, Bihac, Bosnia and Herzegovina

Corresponding author: Mediha Kardasevic, MD. Department of Neonatology. Cantonal Hospital Bihac, E-mail: medihakardasevic@hotmail.com. ORCID ID: http//www.orcid.org/0000-0002-2271-9468.

Infantile Sacral Region Hemangioma and Combination Treatment with Propranolol and Topical Timolol: Case Review and Reference Review

Mediha Kardasevic, Senka Mesihovic Dinarevic

ABSTRACT

Background: Infantile hemangiomas (IH) are the most common vascular, benign tumors of childhood with a prevalence of 4-5%. Due to intense vasculogenesis, they proliferate during infancy, then involute at an unpredictable rate, extent of involution, and quality of residual tissue. Depending on the location, they may be associated with anomalies of other organ systems (PHACE, PELVIS syndroms). In recent decades, knowledge about hemangiomas has improved, and therefore therapeutic possibilities have improved. Today, the non-selective beta blocker–propranolol is considered the drug of first choice in the treatment of infantile hemangiomas. It is desirable to start treatment in the proliferative phase of hemangioma growth for the best possible effect. The dynamics of drug administration, time interval of dose increase and monitoring of patients during treatment vary from one Institution to another and are still the subject of discussion. **Objective:** We presented the case of a child with infantile hemangioma of the lumbo-sacral region, treated with combination therapy with systemic propranolol and topical timolol, with satisfactory effect in the end. **Conclusion:** Propranolol is considered a drug with well-studied side effects and a safety profile. During 6 months of treatment, it leads to complete or almost complete withdrawal of the hemangioma. Treatment should be started in the hemangioma proliferation phase for the best possible therapeutic effect.

Keywords: Infantile hemangioma, propranolol, lumbo-sacral.

1. BACKGROUND

Infantile hemangiomas (IH) are the most common vascular, benign tumor of child bearing age with a prevalence of 4-5% (1). They are not usually present at birth and are diagnosed at 3 to 6 weeks of age. Most of them are self-limiting tumors which, due to intensive vasculogenesis, proliferate rapidly in infancy, then gradually involute, but to what extent and in what time period, it is not possible to predict (2, 3).

IH can be present anywhere on the skin, as surface (superficial), localized deep in the subcutaneous tissue, combined or on internal organs (visceral). Permanent sequelae, such as telangiectasias, redundant or atrophic skin, may remain after hemangioma involution. Sequelae are more common in combined hemangiomas.

Localized in the head and neck area may be associated with PHACE syndrome: P-posterior fossa abnormalities, H-hemangioma, A-arterial anomalies, C-cardiac anomalies, E-eye anomalies (4).

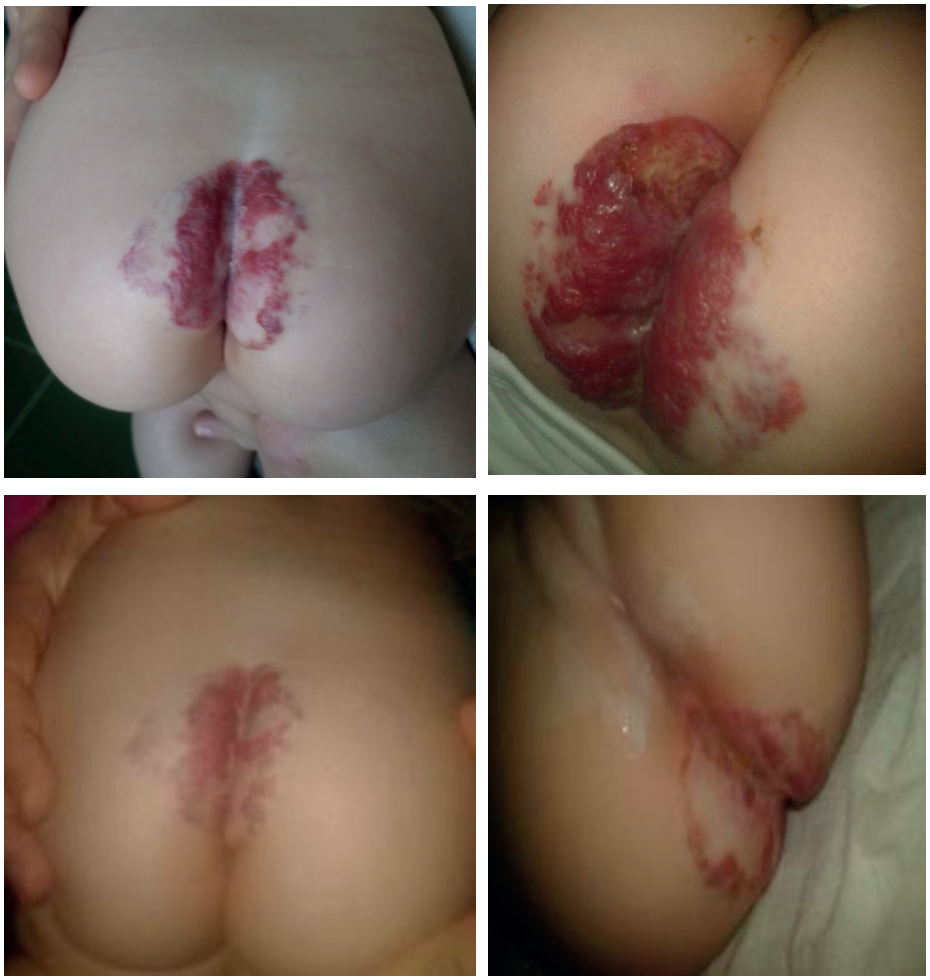
Located in the area of the lumbar or sacral spine may be associated with genitourinary, anorectal, or neurological abnormalities (PELVIS-perineal hemangioma, external genital malformations, lipomyelomeningocele, vesicorenal abnormalities, anus imperforate) (5). Myelopathy, especially spinal dysraphism, is the most common extradermal anomaly in this case (6)

In recent decades, knowledge about IH has improved considerably, which has helped health professionals to promptly identify potentially high-risk IH and cases in which treatment is indicated. Frieden et al. adopted criteria for the treatment of IH: life-threatening hemangiomas or those that lead to functional impairment, ulcerated hemangiomas, hemangiomas in which there is a risk of permanent consequences or scarring (7).

One of the indications for treatment are IH with ulcerations. It is estimated that such hemangiomas range from 5% to 21%. Ulcers can lead to pain, bleeding, secondary infection and ultimately always lead to scarring (8). Therapeutic options for IH include treatment with propranolol, other selective beta blockers, corticosteroids, laser therapy, surgical treatment, topical treatment with beta blockers, and combination therapy.

The positive effect of propranolol on hemangiomas was observed accidentally during the treatment of children for other, cardiac reasons. Since then, numerous studies have been conducted, which examined its efficacy and safety (9-11).

Encouraging results of the treatment of infantile memnagiomas by Léauté - Labrèze et al., in 2008 resulted in a number of confirmatory results by other authors as well (12). Contraindications to the administration of propranolol .re: sinus bradycardia, hypotension, cardiac block greater than grade 1, obstructive bronchitis, heart failure, hypersensitivity to the drug and PHACE syndrome. Since 2014, propranolol has been officially approved for the treatment of IH by the American FDA.



Figures 1-4. Hemangiomas in regression phases during propranolol therapy (Figure 1 and 2) and topical treatment with timolol (Figure 3 and 4)

2. OBJECTIVE

We presented the case of a child with infantile hemangioma of the lumbo-sacral region, treated with combination therapy with systemic propranolol and topical timolol, with satisfactory effect in the end.

3. CASE REVIEW

Female infant Ć.M. At the age of 5 months, was examined by a pediatric surgeon of the Bihać Cantonal Hospital, due to the presence of hemangiomas in the lumbosacral region. Hemangioma with a diameter of 10 x 7 cm, occupied a larger area of the medial part of the said region and both glutes, with exulcerated surface and occasional bleeding. Anamnestic data indicate that the hemangioma was observed at the age of one month and has been in constant progression since then. At the age of 7 months, propranolol therapy was indicated and included by the pediatric cardiologist. Before initiating therapy, values of glycemia, tension, pulse were determined. Clinical examination revealed the absence of obstructive respiratory disease with SatO2 measurement with a transcutaneous pulse oximeter. An ECG record was analyzed to eliminate AV block greater than grade 1 and an ultrasound of the heart to rule out obstructive cardiomyopathy. We received anamnestic data from the mother on possible difficulties with feeding the child or a tendency to bronchial obstructions. As part of the family history, we asked about the existence of a possible AV block in the family. Abdominal ultrasound and LS spine ultrasound were performed in order to exclude possible associated anomalies (PELVIS syndrome). After the tests, we introduced propranolol therapy in an initial dosage of 0.5 mg per kg of body weight, divided into three doses. The mother, motivated for outpatient treatment of the child, was educated to measure heart rate at home, identify potential side effects of therapy, and comorbidities that require propranolol therapy to be discontinued. Monthly check-ups in the cardiology clinic are recommended to assess the clinical condition, measure pulse, tension, glycemia and gradually increase the dose of the drug, up to the target dose of 2 mg per kg of body weight. The treatment lasted 6 months of continuous therapy with propranolol and 3 months of topical therapy with timolol drops in 0.5% concentration, intended for the treatment of glaucoma. No significant side effects were reported. During this period, there was a significant regression of hemangiomas. After treatment, redundant skin was left behind, which we did not

consider a significant cosmetic defect, given the location of the hemangioma.

4. DISCUSSION

Today, propranolol is considered the drug of first choice in the treatment of infantile hemangiomas (13) and its effect on hemangiomas is explained by local, vasoconstrictive action, inhibition of angiogenesis, stimulation of endothelial vascular cell apoptosis, reduction of proangiogenic growth factors: vascular endothelial growth factor and V fibroblast growth factor (bFGF) (14).

During a randomized study in 456 children from the age of 5 weeks to 5 months, with proliferative IH with a minimum diameter of 1.5 cm, were treated with propranolol at a dosage of 1–3 mg per kg body weight or placebo for 3 to 6 months. Patients who received the selected drug showed a significant improvement in 88% of those treated by the end of 5 weeks from drug administration compared with only 5% of patients who received placebo (15).

Treatment is scheduled to begin at the age of 5 weeks to 5 months. It is advisable for the child to be hospitalized briefly if it is younger than 5 weeks, in order to monitor potential side effects. It is evident that some children come to the cardiology clinic late and that it is not agreed which medical team will treat the child (pediatric surgeon, dermatologist, primary care pediatrician, pediatric cardiologist?) In our experience, patients with hemangiomas are most often referred initially to a pediatric surgeon or dermatologist, as a result of which valuable time is lost, since the initiation of propranolol therapy in our conditions is in the domain of the pediatric cardiologist. Prior to the administration of therapy, a comprehensive history and clinical examination of the child is required, as well as additional diagnostic tests to rule out any associated anomalies. Protocols regarding the initial dose and time intervals for increasing it have not yet been harmonized. Monitoring varies from one institution to another. Most hospitals use internal protocols, as there are no harmonized guidelines for drug administration (16).

We monitored the child on an outpatient basis once a month (pulse, weight, ECG, tension, glycemia). The mother is advised to monitor the child's pulse at home for 1-3 hours after drug administration, and to feed the child within 1 hour from drug administration in order to prevent hypoglycemia. Parents are educated on how to recognize the symptoms of hypoglycemia and when to contact a doctor in case the child becomes ill and the symptoms interfere with the administration of the drug (hypoglycemia, hypotension, bradycardia, sleep disorders, diarrhea or constipation, cold extremities).

The risk of side effects is higher in patients with comorbidities. There are no harmonized guidelines for the duration of propranolol treatment, but it is assumed that the optimal treatment period for an adequate therapeutic response is in the range of 6 months of treatment, that is, up to the age of 1 year (17).

A rebound effect, after propranolol therapy, has been observed in numerous studies. Factors contributing to the rebound effect are discontinuation of therapy before the child is 9 months old, female gender, location on the head or neck, involvement of deep skin structures (18).

Topical beta-blockers are used mainly in the treatment of smaller, superficial hemangiomas. They are also often used in combination with the systemic application of beta blockers, especially in order to prevent the rebound phenomenon (19). Topical timolol is most commonly used off-label as a solution for ophthalmic administration at a 0.5% concentration, in the absence of an adequate, registered preparation for the local treatment of infantile hemangiomas. It is applied 2 to 3 times a day, one drop per IH until a stable local effect is achieved. Topical timolol is generally well tolerated and side effects are insignificant unless they are premature babies or children of low birth weight. In this case, the patient is observed for the same potential side effects as with the use of systemic beta blockers.

Since in our case, we started therapy with propranolol late, we decided to continue treatment with a topical preparation, after reaching 13 months of age. A multicenter, retrospective cohort study involving 731 children with superficial IH was treated with topical timolol twice daily. 92% of children showed significant improvement in hemangioma color and 77% of children showed significant improvement in hemangioma size (20), but the positive effect was mainly related to superficial IH. It is questionable how much effect they would have with topical treatment on deep, extensive IH, such as our patient had.

There are studies that have examined the effect of topical timolol maleate in the form of gel or eye drops on IH, and compared it with the effect of systemically administered propranolol. It has been shown that a satisfactory effect can be achieved with topical timolol with very few side effects, and is recommended by some authors as the drug of first choice in the treatment of IH (21). Given that in the market has not been registered composition Hemangiol (suspension propranolol hydrochloride), the children in our institution are treated with propranolol powder in an appropriate dose, made of propranolol tablets. Such off-label administration carries a higher risk of inadequate dosing, concomitant side effects and different availability of the active substance, due to inadequate drug resorption. During the treatment of our patient, no more serious side effects were recorded.

5. CONCLUSION

Propranolol treatment in combination with topical timolol may be effective in the treatment of IH, even when treatment is started outside the recommended time frame. Propranolol is considered a drug with well-studied side effects and a safety profile. During 6 months of treatment, it leads to complete or almost complete withdrawal of the hemangioma. Treatment should be started in the hemangioma proliferation phase for the best possible therapeutic effect.

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- **Conflict of interest**: None declared.
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