

REVIEW

On the dissertation and abstract on

Hemangiomas in Infancy and early childhood - innovative treatment and Follow-up

Presented for public defense before a scientific jury for the award of the degree of Doctor of Science and Education in the field of higher education 7 Health and Sport, professional field 7.1 Medicine in the doctoral program "Dermatology and venerology"

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I have not found any omissions in the documentation attached by Dr. Radka Tsokova Maslarska. I have complied with the requirements of the Law on Academic Degrees and Academic Positions at Acibadem City Clinic UMHAT "Tokuda". I have no conflict of interest from my participation in the scientific jury.

Significance of the topic. Infantile hemangioma (IH) is the most common benign tumor in childhood. Natural evolution is characterized by a period of proliferation in the first months of life, stabilization, and spontaneous involution, which often takes years. There is extreme variability in the size, location, and depth of the hemangioma, which determine the

clinical presentation from life-threatening, requiring immediate treatment to completely benign lesions. IH, especially those located in the face or large areas of the body and extremities are associated with a risk of impaired function, ulceration, pain, and disfigurement. This determines high morbidity and serious psychological problems. Ignorance of the problem and passive waiting by medical professionals and parents' fear of applying modern treatment can lead to irreversible consequences. The treatment of IH was the subject of search and controversy until 2014, when propranolol, a non-selective beta blocker, was accepted by the American and European medical associations as the drug of choice in infancy and early childhood. Hemangiol treatment was introduced and reimbursed by the NHIF in 2018.

In Bulgaria, no systematic studies have been conducted to evaluate the effects of propranolol treatment in infancy and early childhood in children with IH. For this reason, the dissertation work of Dr. Radka Maslarska is relevant and essential for the care of this group of patients in Bulgaria.

Structure. The thesis, written in 155 pages, and includes an introduction (4 pages) literature review (45 pages), aim and objectives (1 page), methodology (5 pages), results and discussion (61 pages), conclusions (2 pages) and recommendations (2 pages). It is illustrated with 32 tables and 80 figures, and 4 appendices. The bibliography includes a total of 163 references, 2 in Cyrillic and 161 in Latin, with 51 % of the cited publications from the last 10 years, and 11 (7%) from the last 5 years.

In the first part of the thesis, which is essentially a **literature review**, the prevalence, the current understanding of the etiopathogenesis of IH, and the main risk factors for its development are discussed in detail. The place of IH in vascular abnormalities as a representative of benign vascular tumors is outlined. Clinical forms, including those associated with rare RHACES and LUMBAR syndromes, and complications of IH such as ulcerations, functional disorders, and deformities are discussed in detail. The indications for further diagnostic investigations as well as current indications for treatment and follow-up of IH are discussed. Special attention is paid to the therapy of IH. Drug therapy is discussed in detail with emphasis on the modern treatment with propranolol. The results of the clinical trials proving the effectiveness and safety of the drug are presented. Dr. Maslarska presents

the steps and stages of preparation for the initiation of treatment, according to the Bulgarian Consensus and the requirements of the NHIF. The historical use of systemic corticosteroids and vincristine, as well as intralesional and topical corticosteroids in the treatment of IH is described. Treatment with topical preparations is discussed, highlighting the lack of standardized indications, as well as studies of systemic resorption and metabolism. The current place of surgical treatment in the treatment of residual lesions and tissue reconstruction, and of laser therapy in the correction of postlesional cicatrices and cosmetic debris is outlined.

Treatment of specific anatomic areas is discussed with emphasis on periorbital and orbital, nasal, oral, perineum, and airway hemangiomas.

The results of randomized trials of the efficacy of Hemangiol 3.75 mg/mL at doses of 1 and 3 mg/kg and durations of 3 or 6 months compared with placebo, led by the inventor of the modern treatment, Dr. Christine Labrez, are presented in detail. These studies demonstrated a clinical effect at a dose of 3 mg/kg for 6 months.

In Bulgaria there are no systematic studies on IH after the introduction and reimbursement by the NHIF of the preparation Hemangiol and Dr. Radka Maslarska set as the **goal** of the thesis, based on a retrospective analysis of infants and young children treated with propranolol, to create an exemplary standard scheme of therapy and follow-up, as well as its introduction into practice in our country.

There are 6 **tasks** that meet the goal:

1. Analysis of factors to determine the correct therapy of vascular malformations.
2. Clinical characteristics of patients treated with Propranolol.
3. Analysis of side effects encountered, need for continued treatment/relapse with Propranolol.
4. Development of a follow-up algorithm for these patients.
5. Analysis and evaluation of the success rate of treatment with Propranolol.

6. Formulation of recommendations and course of action for patients undergoing treatment with Hemangioliol.

Patients and methods. The study included 276 children aged at the start of treatment from 2 months to more than 1 year, diagnosed in the structures of Adjibadem City Clinic Tokuda in the period May 2018 - December 2021, when the criteria of the National Health Insurance Fund for the start of treatment were met.

The main methods used were clinical, including a detailed history of the prenatal, perinatal period, time of onset of IH, and comorbidities. Baseline vital signs (heart rate, respiratory rate, and blood pressure) were assessed and analyzed before initiation, during dose titration, and during treatment continuation. The lesion was described in detail and photo-documented, and the evolution of the hemangioma was reported in dynamic. Laboratory parameters were examined to assess blood counts, blood glucose, and renal and liver function. During the clinical follow-up, the effectiveness of the treatment, duration of treatment, the need for continued treatment, the occurrence of ulcerations, and recurrences were recorded. Modern statistical methods were used to ensure the reliability of the results.

Results. In the characterization of the studied group, Dr. Maslarska found a predominance of the female sex, with 17% of the infants being premature. Multiple hemangiomas were present in 37% of the infants and there was a statistical correlation between multiple hemangiomas, age at birth less than 37 weeks gestational age, weight less than 2500 g, and pathology of pregnancy. The predominant hemangiomas by location were facial (44%), followed by body (22%) and combined (22%), and extremities (11%). There were 193 cases of single IH, 44 cases of two IH, and 23 cases of multiple IH (8.3%). IH was superficial in 49%, deep in 30%, and mixed in the remaining 21%. Ulceration was observed as a complication in 7 patients (2.5%), 3 of them had no response to treatment. Hemangioliol treatment was started before 6 months of age in 71% of infants, which means that it was delayed in 29% of cases. Oral propranolol was used in all infants, and combination treatment was given in 7.6%. After the course, 83.7% of the children were completely cured, in 32 cases (11.6%) changes persisted, requiring continuation of treatment, and in 13 cases (4.7%) there was a relapse. A comparative analysis of the vital

signs of children with two protocols found statistically significant decreases in heart and respiratory rates and increases in arterial pressure. The measured parameters were within reference ranges and can be explained by physiological changes in age rather than the treatment effect. Analysis of biochemical parameters of children with two protocols showed a significant change (increase in ASAT and urea and decrease in ALAT), with values remaining within reference limits, proving that propranolol treatment does not impair liver and kidney function. In the group studied by Dr. Maslarska, the age of treatment initiation had no effect on treatment duration, efficacy, and risk of relapse. Although there is no clear definition of relapse, Dr. Maslarska found changes in vessel depth, vessel density and resistance index in children with relapse. Dr. Maslarska presents an extremely richly illustrated series of photo-documented cases demonstrating the effectiveness of propranolol treatment. Cases with relapse and continued treatment are presented as Appendices 3 and 4.

The **conclusions**, 11 in number, follow the outcome data and statistical analysis and meet the aim and objectives.

Based on the results of the study, Dr Maslarska outlines the following recommendations:

1. To prepare materials for recognizing and taking steps for a therapeutic protocol already in the neonatology wards
2. To use complex medical assessments to determine the need for treatment
3. Transition to palliative care in cases with exhausted treatment options
4. Treatment and follow-up to be carried out by a multidisciplinary team in centers with specialized expertise
5. First choice of treatment is propranolol as an effective and relatively safe agent
6. Studies on IH to continue with the search for additional therapeutic options.

I agree with the contributions presented, with methodological and practical-applied relevance

Submitted are 3 publications, 1 of them in an international journal, which meet the requirements of Adjibadem City Clinic Tokuda EAD.

The abstract meets the requirements of the Academic Staff Development Act.

Critical Notes.

- In order to answer task 1, it would need to review all consulted patients with IH at Acibadem City Clinic Tokuda Hospital and analyze the clinical characteristics and the relative proportion of children who received systemic treatment with propranolol

- The assessment of hemodynamic changes with color Doppler is of interest, but the thesis does not report on how many children a Doppler study was performed

- The bibliography of references 14,64,68,73,105 is incomplete

In **conclusion**, the dissertation work of Dr. Radka Maslarska, based on a retrospective analysis and thorough evaluation of infants and young children with infantile hemangioma treated at Acibadem City Clinic Tokuda Hospital, proves the effectiveness and safety of the modern innovative treatment of this extremely diverse disease. Dr. Maslarska proves that the basis of success is an interdisciplinary approach, in which dermatologists undoubtedly play a major role in diagnosis, but neonatologists and pediatricians are the specialists who conduct, evaluate the treatment, and deal with the administrative, medical, psychological, and other problems and challenges. Fear and unfamiliarity with the disease and the effects of modern treatments are one of the main reasons for passive waiting by medical professionals and parents and delaying therapy, which is very often to the detriment of the patient. Dr Maslarska's extremely rich photographic collection could become the basis for an atlas that would be of practical use to neonatologists, general practitioners, pediatricians, and even dermatologists.

The dissertation work of Dr. Radka Maslarska, lays a solid foundation for the clinical presentation and evolution of infantile hemangioma and allows for the expansion and deepening of studies on specific biomarkers, the pharmacokinetics of oral treatment, as well as standardized topical treatment with drug type, systemic resorption, and metabolism.

The critical remarks made do not diminish the value of the dissertation and this gives me the reason to vote positively and to recommend the members of the scientific jury to evaluate positively the dissertation "Hemangiomas in Infancy and early childhood - innovative treatment and follow-up" and to award Dr. Radka Tsokova Maslarska with the scientific and educational degree of Doctor.

Sofia

24.06. 2023

Reviewed by:



(prof. Anna Kaneva-Nencheva MD)