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O.V. Bogomolets[1,2,3], R.V. Hryshchenko[3], M.V. Pavelko[3], I.O. Krishchenko[3], S.O. Bogomolets–Sheremetieva[3,4]

Analysis of the modern treatment protocols for complicated and uncomplicated infantile hemangiomas. Literature review and own data

[1]Ukrainian Military Medical Academy, Kyiv
[2]Academy of Silesia, Katowice, Poland
[3]Dr. Bogomolets' Institute of Dermatology and Cosmetology, Kyiv, Ukraine
[4]Bogomolets National Medical University, Kyiv, Ukraine

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Infantile hemangioma (IH), a benign tumor of the vascular endothelium, is the most common type of vascular pathology of the infant's skin, which grows and significantly increases in size mostly during the first 12 months of a child's life. Statistics indicate that IH affects up to 10% of newborns and children aged <1 year. The proliferative activity of IHs during the first year of a child's life differs significantly and could mislead parents and doctors. Lack of timely treatment at an early stage leads to an increase in the size of the tumor and high risks of cosmetic defects. Thus, the proliferation of IH can cause a gross deformation of the skin and a dysfunction of nearby organs.

Purpose – to analyze modern data on the treatment of patients with complicated and uncomplicated hemangiomas, to study international experience and compare it with own observations and own experience, and to improve patient treatment protocols.

In this review, we analyzed 19 articles involving more than 2400 children with different types of IH, compared different treatment protocols, their outcomes, and complications, and demonstrated our methods, results, and clinical cases.

It may be resumed that β-blockers are «first-line» drugs for local and systemic treatment of IHs, as they allow slowing of the proliferation and activating resorption of the tumor without cosmetic defects or complications. Treatment of IH in babies following modern treatment protocols should be carried out non-surgically, without operations, anesthesia, scars, or cosmetic defects. Ulceration is the most common complication of IHs and the result of the late start of the treatment and thus could be prevented by the timely beginning of the therapy.

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Keywords: infantile hemangioma, ulceration, treatment, β-blocker, surgery, telemedicine, vascular lasers.

Аналіз сучасних протоколів лікування ускладнених та неускладнених інфантильних гемангіом. Огляд літератури та власні дані

О.В. Богомолець[1,2,3], Р.В. Грищенко[3], М.В. Павелко[3], І.О. Крищенко[3], С.О. Богомолець–Шереметьєва[3,4]

[1]Українська військово-медична академія, м. Київ
[2]Академія Сілезії, м. Катовіце, Польща
[3]Інститут дерматології і косметології доктора Богомолець, м. Київ, Україна
[4]Національний Медичний Університет імені О.О. Богомольця, м. Київ, Україна

Інфантильна гемангіома (ІГ) — доброякісна пухлина ендотелію судин — найпоширеніший вид судинної патології шкіри немовлят, яка проліферує та значно збільшується в розмірах найчастіше протягом перших 12 місяців життя дитини. Статистика показує, що ІГ вражає до 10% новонароджених і дітей віком до 1 року. Проліферативна активність ІГ протягом першого року життя дитини може істотно відрізнятися та вводити в оману батьків і лікарів.

Відсутність своєчасного лікування на ранній стадії призводить до збільшення пухлини в розмірах і високих ризиків появи ускладнень, виразок та косметичних дефектів. Таким чином, проліферація ІГ може викликати не тільки грубу деформацію шкіри, але й порушення функції прилеглих органів.

Мета: проаналізувати сучасні дані щодо лікування пацієнтів з ускладненими та неускладненими гемангіомами, вивчити міжнародний досвід та порівняти його з власними спостереженнями та власним досвідом, вдосконалити протоколи лікування пацієнтів.

Було проаналізовано 19 статей, в яких досліджено понад 2400 дітей з різними типами ІГ, порівняно різні протоколи лікування, їх результати та ризики ускладнень, а також продемонстровано власні методи, результати та клінічні випадки.

Можна резюмувати, що β-адреноблокатори є препаратами «першої лінії» для місцевого та системного лікування ІГ, оскільки дозволяють сповільнити проліферацію та активувати розсмоктування пухлини без косметичних дефектів та ускладнень. Лікування гемангіом у дітей згідно з сучасними протоколами повинно проводитися безопераційним шляхом, без операцій, наркозу, рубців і косметичних дефектів. Виразки є найчастішим ускладненням перебігу гемангіом та виникають в наслідок пізнього початку лікування, отже їх утворенню можна запобігти завдяки вчасному початку терапії.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: інфантильна гемангіома, виразкування, лікування, β-блокатори, хірургія, телемедицина, судинні лазери.

Introduction

Infantile hemangiomas (IHs) are the most common benign vascular tumors in children; the incidence rate ranges from 0.2 to 10.0%. About 60% of IHs are localized on the head and neck. These neoplasms are more common in female infants (5:1 ratio), premature infants weighing less than 1,500 g, and twins [12,29,45]. Usually, IH is detected in the first 2–8 weeks after birth as a red spot. A harbinger of a hemangioma can be a white or pink spot. After the appearance of hemangioma, it begins to increase in size actively. IH has two demarcation lines: 6 and 12 months. During active rapid growth in 2–6 months, the appearance of new hemangiomas, development of local or systemic complications, ulceration, and bleeding are possible [24]. After 6 months, growth continues but slows down. It can be noted: local stabilization of growth, especially in scarring, peripheral or endophytic growth, scarring.

The growth and proliferation of hemangioma lead to thinning of the epidermis and the formation of ulcers that cause pain, create the impossibility of comfortable care and increase the risk of bleeding. Hemangiomas that proliferate to large size can lead to organ and system dysfunction and be part of systemic syndromes.

Moreover, the proliferative activity of IHs during the first year of a child's life differs significantly and can mislead parents and doctors. Tumor growth can be exophytic (growth outward), endophytic (growth in depth), peripheral (increase in size), or combined. Hemangiomas with a tendency toward endophytic growth in some cases require additional instrumental diagnostics: ultrasound and Doppler [24].

After the first year, tumor growth stabilizes for 1–3 years. Some tumors can regress spontaneously. The average rate of regression is 10% of the tumor size per year. The regression term, respectively, is up to 10 years. The larger the tumor, the longer it regresses and the higher the risk of residual cosmetic defects.

Treatment of IH in past years has usually used a watch-and-wait strategy. However, failure to start treatment on time leads to the formation of ulcers, scars, disability, and severe aesthetic defects. Lack of timely treatment of hemangioma located in a critical area may result in irreversible loss of function and disability. Common locations for problematic hemangiomas include the periorbital, oropharyngeal, preauricular, or parotid regions. The lack of timely beginning of the treatment of hemangiomas, which are quickly proliferating, leads to the development of complications and the appearance of pain syndrome. That is why early initiation of IH treatment is the key to successful therapy [37,44]. All the complications can be prevented if hemangioma treatment is started on time.

Ulceration is the most common complication of IH. Ulcerative IHs heal poorly despite wound care, cause pain, bleeding, infection, and sleep disturbances, make feeding difficult for patients, and create disfiguring scars. Therefore, it is crucial to prevent the formation of ulceration – to detect and treat IH in time [35,35].

The use of β-blockers became popular among dermatologists after the discovery of their effectiveness in the treatment of IH [10]. In 2008, S. Léauté–Labrèze et al. first used propranolol in the treatment of IH when they treated a child with nasal hemangioma and hypertrophic cardiomyopathy and accidentally discovered that propranolol could relieve hemangioma symptoms. Since then, physicians have switched to propranolol for children with IH and have achieved good clinical results [23]. Systemic oral propranolol hydrochloride was approved by the FDA in 2014 for the treatment of proliferating IH located near the eyes, mouth, or those that carry a risk of disability to the child. Since then, β-blockers have become the first-line drug for the treatment of complicated hemangiomas, especially ulcerated ones.

Propranolol (anaprilin) is a cardiac drug — a non-selective blocker of adrenoreceptors — whose presence has been confirmed in the endothelial cells of hemangiomas. The state of receptors at different stages of the develop-

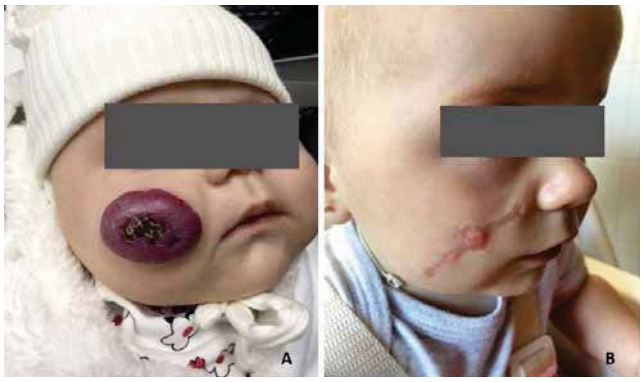

Fig. 1. Photos of the child with complicated IH, surgery treated. Gender F. A – At the age of 2.5 months; B – Scar after surgical excision of IH at 4 months

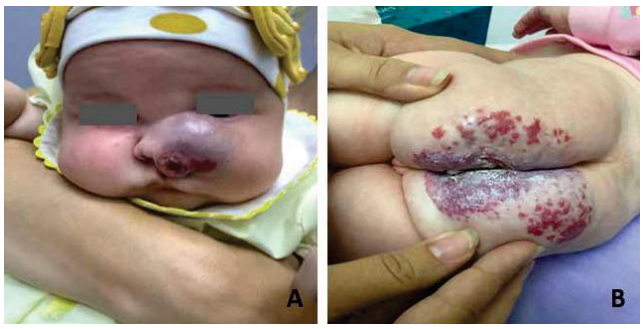

Fig. 2. Cases of IH complicated with ulceration. A – Gender F. 3 months, 16 days. Localization: nose and left cheek; B – Gender F. 3 months, 18 days. Localization: buttocks and anus area

ment of hemangiomas and in control tissues is different, which determines the greater or lesser sensitivity of IHs to treatment. Among the mechanisms of the influence of β-blockers on vascular tumors, the following are highlighted: blocking angiogenesis, inducing apoptosis, inhibition of nitric oxide production, acceleration of the transformation of hemangioma stem cells into adipocytes, and influence on the renin-angiotensin system.

A significant improvement in the condition of children with complicated IH who were treated with propranolol was noted. The effectiveness of oral propranolol in the treatment of IH is based on the results of randomized controlled trials, which confirm a 60% success rate compared to 4% for patients treated with a placebo [30]. M. Hasan et al. (2013) administered propranolol orally to 36 children with IH at a dose of 3 mg/kg/day in three doses. An immediate effect on color and size was observed in all cases, which was particularly important in cases of widespread lesions. Clinical signs of regression were observed within 30 days in all patients, and they completely regressed within 7 months. The average duration of treatment was 4.1 months. According to the authors' conclusions, propranolol had a rapid stabilizing effect, leading to early regression of hemangiomas when administered orally [18].

However, approximately 13.7% of patients treated with oral propranolol experienced systemic side effects [30]. Sleep disturbances, drowsiness, irritability, bronchospasms, bronchiolitis, hypotension, bradycardia, atrioventricular block, gastrointestinal disorders, and hypoglycemia may occur.

Zhang et al. (2017) performed sonography before propranolol treatment to detect any possible congenital heart defects [45]. Patients were treated on an outpatient basis for 6 months. To minimize complications, oral propranolol was used once daily at a dose of 1.0 mg/kg for children under 2 months of age and twice per day at a total daily dose of 2 mg/kg for patients older than 2 months. In the last month of treatment, the dose of propranolol was halved during the first 2 weeks. If there was no deterioration, the dose was reduced by half until the treatment was completely stopped. Five hundred sixty (96.9%) of 578 patients with IH responded to oral propranolol treatment, but the response rate varied significantly among children of different ages, with the youngest patients having the highest response rates. Thus, the response rate to propranolol was 98.1% in patients younger than 2 months, 93.3% in patients aged 2 to 8 months, and 73.7% in patients older than 8 months. One hundred and thirty-one patients with incomplete involution of IH were additionally treated with 0.5% timolol maleate solution (n=89) or pulsed laser (n=42); 117 (89.3%) of them had a positive response. There were no life-threatening complications. However, minor side effects were observed: 10 (1.73%) cases of sleep disturbance, 7 (1.21%) cases of diarrhea, and 5 (0.86%) cases of bronchospasm. The authors emphasize that IH requires early intervention, and the sooner treatment begins, the better the effect will be, which can minimize the frequency of complications [45].

While the effectiveness of propranolol in the treatment of complicated IH is convincing, questions regarding the use of other β-blockers, topical administration, the mechanism of action, risk stratification before treatment (treatment usually begins with observation of the child's vital functions in an inpatient or outpatient setting), and optimal dosing continue [17].

It is important to note that surgical excision is no longer used in the treatment of IHs due to the risks of general anesthesia, blood loss, a long rehabilitation period, scarring, and the risk of recurrence. Injections of steroid hormones and cryodestruction are also not recommended, as they leave atrophic scars, changes in skin texture, and baldness [42].

Thus, despite the long-term treatment with topical β-blockers and possible side effects during therapy with systemic β-blockers, surgery in IH should be avoided.

This clinical case demonstrates all the disadvantages of this method: scarring, facial disfigurement, and a negative psycho-emotional impact on the child (Figure 1).

Complications of IH by ulceration can lead to pain, bleeding, infection, or scarring [27]. The practice of combining treatments is common: local wound care, pulsed dye laser, infection control, suppression of bleeding, etc. However, doctors should direct efforts to prevent the formation of an ulcer, for this purpose, it is necessary to start treatment with β-blockers in time.

Here are some cases that demonstrate IHs complicated with ulceration and disfigurement that could be prevented if the treatment was started in time (Figure 2).

In this review, our purpose was to analyze data from the literature devoted to the methods of using various β-blockers in complicated and uncomplicated IH, determine the optimal protocols for the treatment of IH of different degrees of risk, assessed the practicality and effectiveness of topical use of β-blockers, and presented data from our own clinical experience in the use of β-blockers in complicated and, in particular, ulcerated IH.

We analyzed 19 literature reviews and clinical studies published in PubMed and MEDLINE during the 2008–2022 period, where the use of local β-blockers in IH was studied, including treatment carried out in hospital and outpatient conditions. This made it possible to conclude the effectiveness of various topical treatment methods and optimal indications for their appointment, determine the frequency of complications, and compare various topical preparations used for the treatment of IH, including complicated forms with high and the highest levels of risk.

In general, reviewed articles (including reviews, meta-analyses, clinical trials, and cases) involved more than 2400 children (ages from birth until 16 months) with different types of IH (from superficial to extensive and complicated with ulceration). IH was treated with nadolol, propranolol, and timolol maleate in different forms (ointment, cream, gel, and eye solution) and doses. We compared different treatment protocols, their outcomes, and complications, and demonstrated our methods, results, and clinical cases.

Informed consent of the patients (parents of the children or their guardians) was obtained for conducting the research and publishing the results.

According to modern treatment tactics, it is necessary to correctly diagnose IH and choose the appropriate treatment according to the age of the child and the degree of risk of hemangioma.

Nowadays, oral propranolol (a nonselective β-blocker) is currently considered a first-line drug for complicated IH requiring systemic treatment. Propranolol has been documented to cross the blood-brain barrier, with potential long-term neurocognitive and other effects. Reported side effects of propranolol in the treatment of IH also include symptomatic hypoglycemia and bradycardia. Numerous adverse reactions prompted scientists to evaluate different β-blockers in the treatment of IH [20,22].

Other β-blockers (acebutolol, atenolol, captopril, and nadolol) have been studied as alternative methods of treating IH [21]. Thus, E. Pope et al. (2013) published a pilot study to examine the efficacy and safety of nadolol (a non-selective β-blocker used in pediatric practice for the treatment of cardiovascular disease) by comparison with a cohort treated with oral propranolol. At similar mean doses (2.1 mg/kg/day), 10 patients receiving nadolol had a mean (SD) IH involution of 51% (18.5%) during 4 weeks of treatment, 83% (13.9%) during 12 weeks, and 97% (3.5%) at the end of the study (24 weeks). In contrast, the 10 propranolol-treated patients had SD IH involution of 28% (10.4%), 56% (16.6%), and 86% (14.8%) at 4, 12, and 24 weeks, respectively. Nadolol was well tolerated without significant side effects [33].

In another study (2022), the authors used nadolol to treat children who had no response or side effects to propranolol. Infants aged 1 to 6 months with IH greater than 1.5 cm on the face or 3 cm or greater elsewhere on the body, causing or likely to cause functional impairment or cosmetic disfigurement, were prescribed propranolol (n=36) and nadolol (n=35) orally in doses up to 2 mg/kg/day. More patients in the nadolol group achieved 75 and 100% involution compared with patients in the propranolol group. Most patients experienced at least 1 adverse event (77.1 vs. 94.4% at 0 to 24 weeks and 84.2 vs. 74.2% at 24 to 52 weeks in the nadolol and propranolol groups, respectively). Efficacy data, combined with a more predictable pharmacokinetic profile and a lower probability of crossing the blood-brain barrier, may make nadolol an alternative to propranolol for patients with IH [34].

Furthermore, clinicians began to use topical β-blockers. Of the 302 children with IH observed between 2008 and 2010, 15.6% received oral propranolol alone, 5.6% received topical timolol alone (0.5% timolol maleate gelling solution), and 2.3% received both. The use of these drugs increased from 7% of patients seen in 2008 to 54% of patients treated in 2010 [4]. The most common local β-blockers used in IH are propranolol and timolol (0.5% gelling solution of timolol maleate). Although topical timolol maleate is used more often than topical propranolol due to its already-known use in ophthalmology, it was concluded that there is no significant difference between topical timolol and propranolol in the treatment of IH [30]. According to the lite-

rature review published by M. Novoa et al. (2018), there were no differences between oral propranolol at a dose of 1 mg/kg/day and topical 0.5% timolol (three times daily) in the ability to reduce lesion size by 50% or more.

A systematic review of more than 700 patients with superficial IH showed no significant difference in clinical improvement between topical 0.5% timolol maleate hydrogel (three times daily) and oral propranolol 2 mg/kg/day), including cases with IH greater than 5 cm^2. Both oral propranolol and topical timolol provided satisfactory therapeutic results, with effective response rates of 97 and 96.4%, respectively. The rate of systemic side effects in patients treated with oral propranolol (3.9%) was significantly higher than in patients treated with topical timolol (0%). Twelve patients treated with timolol experienced mild local side effects, including pruritus and skin rashes. Clinical response was not associated with sex, duration of treatment, site of lesion, size of lesion, gestational age, or use of progesterone during pregnancy but was associated with age at initiation of treatment, indicating that younger age at initiation of treatment predicts better and faster IH regression [41].

Consequently, the use of topical β-blockers was initiated, intending to reduce the systemic side effects of propranolol. Topical β-blockers are now used to treat IH with both deep and superficial components. If treatment is started in the proliferative phase of the lesion, the effect can be seen within a few days. 1% propranolol ointment is also available; it is less well studied, but reports suggest that the ointment provides similar results to topical timolol. However, there is no consensus on the dosage, bioavailability, or clinical evaluation of lesions treated with topical β-blockers, which are topics for future research [5,32].

Even if topical β-blockers are an effective alternative to oral ones in the treatment of IH with both deep and superficial components, it cannot be excluded that they may be systemically absorbed, leading to a possible risk of side effects [7]. However, the exact concentration of β-blockers in the affected area is difficult to determine precisely, and an uncertain concentration can lead to insufficient or dangerously high levels of the drug, especially in patients at potential risk. Thus, after Holter monitoring to assess drug-induced bradycardia in 22 high-risk infants receiving topical timolol (both solution and gel), P. Frommelt et al. (2016) found that topical timolol provided safe treatment of IH in term infants at a dose of less than 0.2 mg/kg/day. For infants weighing less than 2500 g at baseline, there was a possible risk of adverse effects, including bradycardia, arterial hypotension, apnea, and hypothermia. The authors recommend careful monitoring of temperature, blood pressure, and heart rate in preterm and low-birth-weight infants at the beginning and during topical timolol therapy [13].

Topical β-blocker therapy is not currently standardized or approved for use by the US Food and Drug Administration. Indications for local therapy with β-blockers are considered to be the presence of a patient with a developed hemangioma that causes a functional deficit, for example, an IH located near the orbit or in the respiratory tract, as well as cases of significant cosmetic deformity or ulcers [5].

In one of the first studies, A. Chakkittakandiyil et al. (2012) reviewed treatment with a topical β-blocker (timolol maleate 0.1% or 0.5% solution) in 73 patients with IH. The average age of children at the beginning of treatment was 4.27 months, and the duration of treatment was 3.4±2.7 months on average. Most children had superficial hemangiomas, and >95% showed improvement in appearance as measured by the visual analog scale (VAS). The predictors of a better response were the superficial type of hemangioma, the concentration of 0.5% timolol, and the duration of treatment for more than 3 months. Among the children, 1 patient did not respond to therapy, and 1 had the side effect of poor sleep, so treatment was discontinued [9]. A. Tawfik and J. Alsharnoubi (2015) compared the treatment of 60 patients with superficial and mixed IH with topical timolol and Nd: Yag laser. Improvement was determined with the help of experts who evaluated photographs and skin parameter analyzer scores. Hemangiomas with a deep component responded better to laser therapy. Superficial hemangiomas gave an «excellent» response in 40% of patients treated with topical timolol, and a «mild» improvement was noted in 90% [38].

Regarding topical propranolol, many topical preparations are used in clinical practice, including 1% propranolol gel, 2% propranolol cream, and 4% propranolol gel [11]. The results, in all cases and for all tested concentrations, are indeed encouraging, as a corresponding clinical improvement (partial to excellent) was registered in 147 of 148 patients treated with 1% propranolol gel twice daily for 12 weeks [11]. As well as in 23 of 40 patients treated with 2% propranolol cream three times daily [39] and in 62 of 75 patients treated with 4% propranolol gel twice daily [26]. In 2015, the results of a meta-analysis evaluating the evidence for the topical use of β-blockers in the treatment of superficial IH were published. A total of more than 550 patients were enrolled, and only one systemic adverse event (poor sleep) was reported. The percentage of response to treatment was 80%. A subanalysis concluded that there was no significant difference between topical propranolol and topical timolol [31].

H. Gong et al. (2015) compared the clinical effects and safety of oral propranolol, topical timolol maleate, and their combination in treating superficial IH (n=39). Patients were randomized into 3 groups of 13 each: the group 1 received topical timolol maleate with oral propranolol, the group 2 received oral propranolol alone, and the group 3 received topical timolol maleate alone. The maximum duration of treatment was planned for 6 months. The overall clinical efficacy score for the three groups was 11/13, 9/13, and 8/13, respectively. The two drugs together provided a shorter effective response time than when administered alone. There were no serious side effects. The authors conclude that topical timolol in combination with oral propranolol is safe and effective in the treatment of superficial IH. Compared to traditional treatment, this method is faster, has a tangible effect, takes less time, and has fewer side effects. It can be used as a first-line treatment, especially if the lesion is potentially disfiguring or functionally threatening [16].

H. M. Marey et al. (2018) evaluated the safety and efficacy of combined treatment with oral and topical β-blockers of superficial periocular IH in the early proliferative stage (n=25). The combination treatment group received oral propranolol (initially 1 mg/kg per day, gradually increased over 2 weeks to 2 mg/kg per day) and 0.5% timolol gel. The systemic-only group received the same dose of oral propranolol and a simple topical eye ointment. Regarding treatment response, 10 and 3 cases in the combination and systemic treatment groups, respectively, showed a good response. No serious local or systemic complications were reported in either group [25]. At the same time, for a long time, it was believed that local therapy with β-blockers did not provide for the treatment of ulcerative IH [5].

A combination of oral and topical β-blockers has been studied for the treatment of complicated hemangiomas with excellent results. J. Ge et al. (2016) conducted a retrospective study of 89 patients with complex IH treated with both oral propranolol 2 mg/kg/day, 1 mg twice daily) and topical timolol (0.5% timolol maleate gel three times per day) for at least 3 months. At the end of treatment, this combination therapy provided a clinical response in 100% of patients. The baseline hemangioma score before treatment was 8.67 and at the end of treatment was 2.07, indicating that hemangioma involution was statistically significant. The response of IH to therapy depends on her age at the start of treatment. Of the 89 patients, complete resorption of the hemangioma occurred in 19 (21.3%) children, almost complete in 41 (46.1%) children, moderate in 18 (20.2%) children, mild in 7 (7.9%) children, and the minimum in 4 (4.5%) children. The first noticeable effects of the combination therapy were the fading of the color as well as the softening of the lesions. One (1.1%) patient relapsed after stopping the 6-month treatment, and 7 (7.8%) children developed side effects: cold extremities (n=3; 3.4%), agitation at night (n=2; 2.2%), and diarrhea (n=2; 2.2%). The study strongly suggested that oral propranolol in combination with topical timolol is a very effective treatment for complex IH, is well tolerated by patients, and can be recommended as first-line treatment. However, the literature on combination therapy is very limited, and there is no consensus on the appropriate way to use and monitor such therapy in children with complex IH [14].

The duration of therapy depends on the degree of damage and sensitivity to treatment. In the study by D.J. Hermans et al. (2013), propranolol was used for the treatment of 174 children with complicated IH for an average of 10.7 months [19]. In the other study [14], the average duration of treatment was 6.48 months, indicating that combination therapy can shorten the course of treatment.

Currently, there is no generally accepted protocol for the initiation, dosing, and monitoring of topical timolol treatment. Since timolol is 4–10 times more potent than propranolol, the total dose of oral propranolol and topical timolol should be considered [28]. In general, percutaneous systemic absorption of most topical drugs is only a small percentage of the total amount of the drug. An estimate of the systemic bioavailability of 5–10% topical timolol gives an equivalent dose of oral propranolol of only 0.2–1.0 mg or 0.05–0.25 mg/kg, respectively, for infants weighing 4 kg (0.03–0.17 mg/kg for babies weighing 6 kg) [3]. These estimates suggest a much lower need for caution, and systemic side effects of topical timolol are unlikely. However, until full safety testing is completed, combination therapy should be used with caution, especially in premature infants and in IHs that occupy a large body surface area [14]. L. Weibel et al. (2016) measured the systemic absorption of timolol in both urine and blood samples. Although levels of timolol were present in all analyzed samples, no systemic side effects were observed, indicating that systemic absorption of the drug does not reach potentially dangerous levels [40].

Optimizing the topical use of propranolol is a difficult issue in clinical practice, as not only the concentration but also the composition can affect the penetration, absorption, and even delivery of drugs to the affected area. In particular, A. Casiraghi et al. (2016) focused on four types of topical 1% propranolol preparations (hydrophobic ointment, two lipophilic creams, and a hydrophilic cream), showing that the highest levels of propranolol

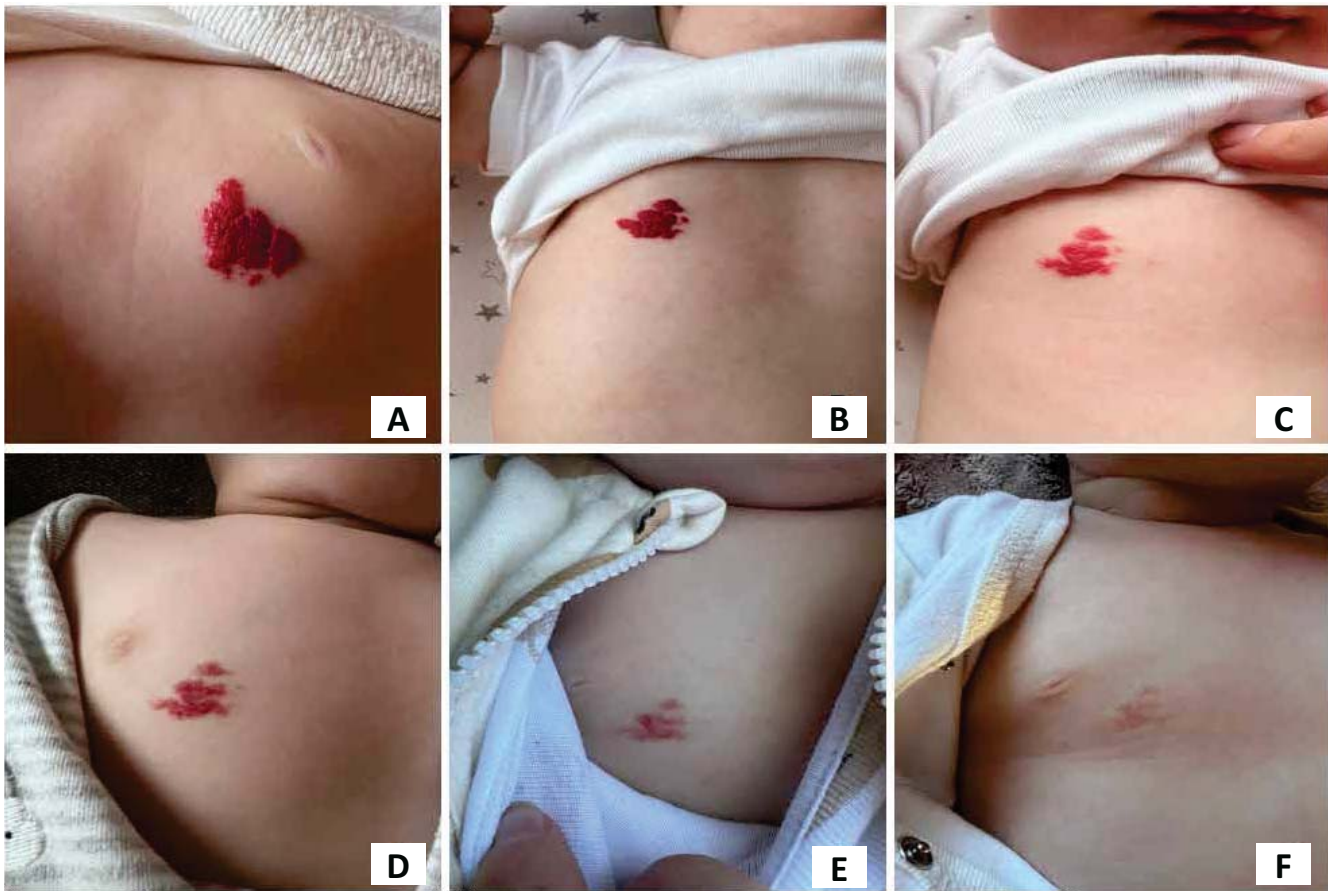

Fig. 3. The IH's resorption process: A – before treatment at the age of 2 months; B – one-week treatment with topical timolol 1% gel; C – one-month treatment; D – two-month treatment; E – three-month treatment; F – five-month treatment

penetration through the skin are guaranteed when a hydrophilic cream is used [8].

In our clinic, to determine the optimal method of treatment, we use data on the degrees of risk of IH to quickly and efficiently determine the protocol for the use of various types of β-blockers.

At the highest degree of risk, the size of the tumor exceeds 5 cm, or the tumor is segmental, or located next to physiologically important openings. When located on the face or head, on the neck or chin, there is a high risk of disruption of vital functions; it can be associated with PHACE syndrome (posterior fossa brain malformation, segmental hemangiomas of the head and neck, arterial anomalies, coarctation of the aorta or cardiac defects, and eye anomalies). Immediate additional examination and the prescription of systemic β-blockers are recommended. If necessary to speed up the absorption, use local β-blockers as well.

A hemangioma located near vital openings in any location with high-growth rates and a child under 6 months of age is considered high-risk. Further examination and appointment of local or systemic β-blockers are recommended.

A hemangioma of any localization is considered to be of medium risk at the age of a child under 6 months. In this case, treatment with local β-blockers and a special vascular laser is possible in combination with local β-blockers after the end of the proliferation phase to accelerate the lysis of pathological vessels.

Hemangioma is considered low-risk when the child is older than 6 months and the tumor is far from vital organs. Local treatment with β-blockers and vascular lasers can be recommended to accelerate the lysis of pathological vessels. Observation is possible.

The effectiveness of treatment with β-blockers directly depends on the age of the child at the time of treatment because the sensitivity of the hemangioma to β-blockers is highest in the hemangioma's growth phase and decreases during the first year. Thus, at the age of 1.5 years (±6 months), a hemangioma ceases to be sensitive to β-blockers; therefore, the treatment loses its effectiveness. The optimal time to start treatment of hemangioma with β-blockers is up to 2 months before the beginning of the greatest proliferative activity. In the case of starting treatment at the age of 2 months, β-blockers manage to stop proliferation and achieve complete regression of the tumor within 10–12 months. In the case of starting treatment at the age of 3–6 months, β-blockers may not have time to achieve complete tumor regression for up to

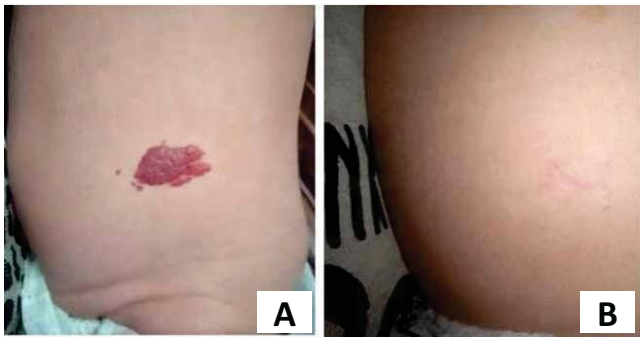

Fig. 4. IH on the left side of the trunk was treated with topical 1% timolol maleate gel: A – photo taken during the first visit at the age of three months; B – photo taken after 10 months of treatment

Fig. 5. The result of IH treatment with topical β-blockers. The photo of the patient before (A) and after a 5-month course of treatment with topical timolol maleate 0.5% (B)

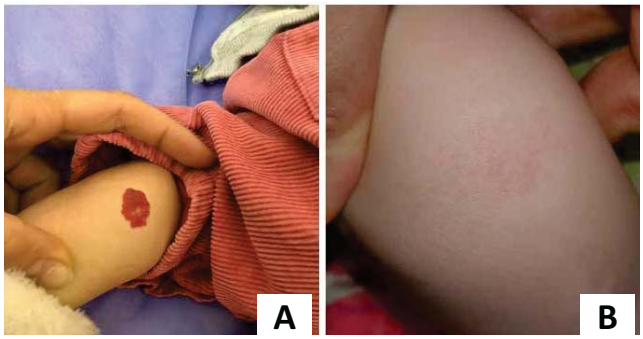

Fig. 6. Patient with IH of the left lower leg at the time of the first visit to the clinic in 2 months (A) and after 11 months of treatment with topical β-blocker timolol maleate 0.5–1% (B). All treatment was carried out online, there was only one visit to the clinic

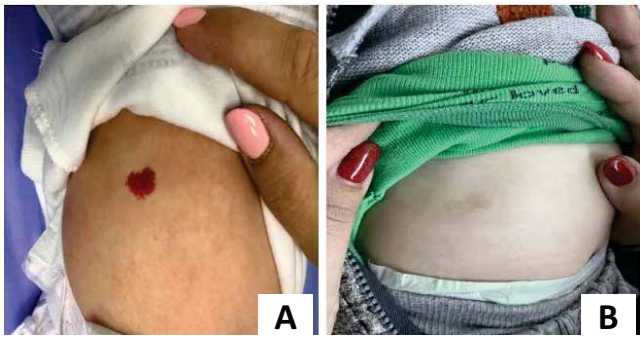

Fig. 7. The result of treatment of IH with topical β-blocker timolol maleate 0.5–1% and a special pulse dye laser (VBeam Perfecta «Candela» 595 nm), 4 procedures. At the treatment beginning, the child's age was 2 months (A), now the child's age is 10 months (B)

1.5 years. When starting treatment at the age of 6–12 months, to achieve complete regression, it will be necessary to add laser technologies.

Resorption of IH during treatment with local β-blockers begins without reducing the size of the tumor but with changes in color of IH, and has three stages (usually 2–4 months each):

- slowing down the hemangioma growth — a decrease in the intensity of the red color and stopping the growth of the tumor;
- germination of connective tissue — the appearance of a white net all over the surface of the hemangioma;
- complete absorption of pathological vessels and restoration of the normal texture of the skin and its appendages (Figure 3).

At the same time, the speed of the tumor absorption rate during treatment with local β-blockers depends on the activity of the tumor. Treatment of hemangioma in infants with local β-blockers may last up to 12–18 months of the child's age and should not be interrupted because it has a cumulative effect. The dosage selection of local β-blockers and the frequency of treatment depends on the age and weight of the child and the location and size of the tumor.

We have been using a group of β-blockers in various dosages and forms for more than 10 years in our practice in the management of complicated IH with the highest, high, and medium-risk groups. The topical β-blocker in the form of a gel containing timolol maleate at concentrations of 0.25%, 0.5%, and 1% proved to be the most efficacious treatment option for local treatment (Figure 4). The sterilization of this product allows it to be used for ulcerated IH healing, and the precise dosage of IHs near the eyes and on the mucus membranes ensures the safety of the child.

In the case of the early beginning of the treatment, timolol maleate allows an effective cure even for big IH without causing scarring or disfigurement, as we proved by our clinical cases (Figures 5, 6, 7).

In a recently published article, we highlighted the effectiveness of β-blocker timolol 0.5% sterile solution in the ulcerated IH [6] treated by the telemedicine store-and-forward method. As far as the child was in the occupied territories of the Kherson region, hospitalization, and inpatient treatment were refused due to shelling, and the parents could not take the child out to the safe region – telemedicine was used.

At the time of the first e-consultation, the IH had spread to a third of the right shoulder and was com-

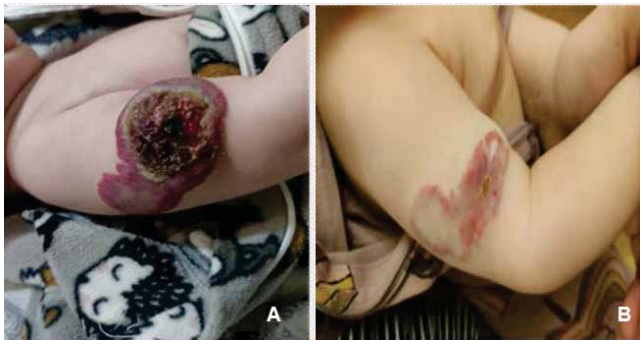

Fig. 8. Photo of the IH, complicated with ulceration and secondary infection: A – before the treatment with β-blocker 0.5% timolol maleate sterile solution; B – after 8 months of treatment (β-blocker treatment was not finished yet at that moment)

plicated by ulceration and secondary infection (Figure 8).

It was prescribed: azithromycin suspension and daily dressing with Grassolind and Octenisept for 5 days. The state of the wound was controlled daily with photos and videos taken by the parents. On the 6th day, we started topical treatment with β-blocker 2 drops timolol 0.5% sterile solution on the IH ulcerated surface, plus 1–2 drops for the un-ulcerated part and a b.i.d. Hydrocoll bandage on top. During treatment, a gradual improvement of the wound condition was recorded without any side effects. After 8 months of treatment, complete re-epithelialization was achieved, but the timolol treatment was continued and combined 4 treatments with pulse dye laser (VBeam Perfecta «Candela») until the hemangioma completely regressed.

Conclusions

From the data of the analyzed literature and our results, it can be concluded that:

1. Ulceration is the most frequent complication of IH in the proliferative phase, which leads to cosmetic defects and scars.

2. Ulceration of the IH can be prevented by timely beginning of topical treatment.

3. Surgical treatment leaves a cosmetic defect and traumatizes the child physically and psycho-emotionally, and therefore it should not be the method of choice for treatment of IH.

4. The use of systemic and topical β-blockers gives a confirmed high therapeutic and cosmetic effect in uncomplicated IH and IH complicated by ulceration.

5. The choice of method should be individualized based on the patient's specific circumstances and the hemangioma's characteristics and, if necessary, can be combined with other treatment approaches.

6. The best and optimal time to start topical treatment with β-blockers is 2 months before the beginning of active proliferation.

No conflict of interests was declared by the authors.

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Відомості про авторів:

Богомолець Ольга Вадимівна *– д.мед.н., проф. Української військово-медичної академії, науковий консультант медичного факультету Академії Сілезії (Катовіце, Польща), головний лікар Інституту дерматології і косметології доктора Богомолець. Адреса академії: м. Київ, вул. Князів Острозьких, 45/1, корпус 33; тел.: +38 (044) 280–01–43. https://orcid.org/0000–0001–7869–8443.*

Грищенко Роман Вадимович *– доктор філософії, лікар-дерматовенеролог, дерматоонколог Інституту дерматології і косметології доктора Богомолець. Адреса: м. Київ, бульвар Т. Шевченка, 26/4б; тел.: +38 (044) 235–00–08.*

Павелко Марія Валентинівна *– лікар-дерматовенеролог, дерматоонколог Інституту дерматології і косметології доктора Богомолець. Адреса: м. Київ, бульвар Т. Шевченка, 26/4б; тел.: +38 (044) 235–00–08.*

Крищенко Ірина Олександрівна *– лікар-дерматовенеролог, дерматоонколог Інституту дерматології і косметології доктора Богомолець. Адреса: м. Київ, бульвар Т. Шевченка, 26/4б; тел.: +38 (044) 235–00–08.*

Богомолець–Шереметьєва Софія Олексіївна *– студентка медичного факультету НМУ імені О.О. Богомольця; адміністратор Інституту дерматології і косметології доктора Богомолець. Адреса: м. Київ, бульвар Т. Шевченка, 26/4б; тел.: +38 (044) 235–00–08.*

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