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Treatment of infantile hemangioma with topical β-blockers in pediatric practice: a review of the literature

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The purpose of this review is to acquaint the audience with the benefits of infantile hemangioma (IH) treatment with local β-blockers, which are safe for the child, allow for the complete cure of hemangiomas without surgery, complications, scars, and cosmetic defects, and have practically no systemic side effects. We aimed to analyze the effectiveness and limitations of the use of local β-blockers, to show the possibility and expediency of IH management in pediatric practice, and to demonstrate that the goal of therapy is not the treatment of complications, but the prevention of their occurrence and complete resolution of the hemangioma without surgical intervention.

The use of topical β-blockers, such as timolol gel or solution, provides a non-surgical, non-invasive treatment option for IH, minimizing the systemic exposure and possible side effects associated with oral β-blockers. Local treatment is best started before the age of 2 months — at an early stage, when IHs are small in size, potentially preventing the need for more invasive treatment methods.

Topical use is associated with a lower risk of systemic side effects, such as hypotension or bradycardia, that can occur with oral β-blockers. Topical treatment can be applied at home, which can be more convenient for parents and caregivers, and also increases the opportunity for treatment and follow-up by pediatricians. In case of natural disasters or military operations, treatment can be done remotely using teledermatology.

The effectiveness of local β-blockers mostly depends on the age at which treatment was started: the earlier it was started, the higher the effectiveness. Treatment of complicated IH with deep soft tissue, mucosal, or airway involvement usually requires a combination of systemic propranolol and topical β-blockers or other interventions such as laser therapy.

The choice of treatment should be selected individually according to the degree of risk of IH, its size, localization, child's age, weight, and other parameters in each clinical case.

β-adrenoblockers are the most modern, effective, non-surgical, and safe method of treating IH, they can be used both for systemic and local application. IH can be successfully treated by pediatricians and dermatologists.

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Keywords: infantile hemangioma, hemangioma treatment, local β-blockers, timolol.

Лікування інфантильних гемангіом місцевими β-блокаторами в педіатричній практиці: огляд літератури

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Метою даного огляду є ознайомлення аудиторії з перевагами лікування інфантильних гемангіом (ІГ) місцевими β-блокаторами, яке є безпечним для дитини, дозволяє повністю вилікувати гемангіому без хірургічного втручання, без ускладнень, рубців , і практично не має системних побічних ефектів. Ми ставили за мету — проаналізувати ефективність та обмеження застосування місцевих β-блокаторів, показати можливість і доцільність ведення ІГ в педіатричній практиці та продемонструвати, що метою терапії є не лікування ускладнень, а попередження їх виникнення та повне розсмоктування гемангіоми.

Використання місцевих β-блокаторів, таких як гель або розчин тимололу, забезпечує безопераційний неінвазивний варіант лікування ІГ, мінімізуючи системний вплив і можливі побічні ефекти, пов'язані з пероральними β-блокаторами. Місцеве лікування краще розпочинати у віці до 2-х місяців — на ранній стадії, коли ІГ невеликі за розміром, що потенційно запобігає потребі у більш інвазивних методах лікування.

Місцеве застосування асоціюється з меншим ризиком системних побічних ефектів, таких як артеріальна гіпотензія або брадикардія, які можуть виникати при пероральному застосуванні β-блокаторів. Місцеве лікування можна застосовувати вдома, що може бути зручнішим для батьків і опікунів, а також збільшує можливість лікування і спостереження у педіатрів. У разі стихійних лих або військових дій лікування може бути дистанційним за допомогою теледерматології.

Ефективність місцевих β-адреноблокаторів здебільшого залежить від віку, в якому було розпочато лікування: чим раніше розпочато – тим вища ефективність. Лікування ускладнених ІГ із ураженням глибоких м'яких тканин, слизових оболонок або дихальних шляхів зазвичай потребує комплексного застосуваня системного пропранололу та місцевих β-блокаторів або інших втручань, таких як лазерна терапія.

Вибір лікування має підбиратися індивідуально відповідно до ступеня ризику ІГ, її розміру, локалізації, віку дитини, ваги та інших параметрів у кожному клінічному випадку.

β-адреноблокатори є найсучаснішим, ефективним, безопераційним і безпечним методом лікування ІГ, їх можна використовувати як для системного, так і для місцевого застосування. Лікування ІГ можуть успішно проводити педіатри та дерматологи.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: інфантильна гемангіома, лікування гемангіом, місцеві β-блокатори, тимолол.

Introduction

The most common benign vascular tumor in childhood is infantile hemangioma (IH), which is found in approximately 4–5% of children in the first year of life [15]. IHs were distinguished from other congenital vascular anomalies by J.B. Mulliken and J. Glowacki (1982) based on the discovery of their unique characteristics: absence at birth, passage through a phase of increased cellular proliferation, followed by a phase of involution, and, ultimately, regression over time [24].

Recent studies have shown an increase in the incidence of IH in the population over the last decades, which correlates with indicators of low birth weight, as well as an increase in the number of premature births and pregnancy complications [2]. The anatomical location of IH can have prognostic consequences and cause impairment of vital functions (for example, respiratory or visual obstruction), scar formation, and/or disfigurement of the affected areas, which not only affects the appearance and psychological state but also poses a potential threat to life [5,34].

While many IHs resolve on their own without causing complications, some can present challenges. The percentage of complications associated with IHs can vary widely depending on factors such as the location, size, and characteristics of the IH.

The frequency and types of complications associated with IHs can vary widely from one case to another [6]. Here are some of the potential complications and their relative frequencies:

— *Ulceration:* Approximately 10–15% of IHs can ulcerate, typically when they are large or located in areas of high friction, such as the diaper area or the neck. Ulceration can lead to pain, infection, and scarring.

— *Functional impairment:* The location of the IH can affect vital functions. For instance, an IH near the eye might cause visual obstruction, while one near the mouth or nose may interfere with feeding or breathing. Functional impairment is less common but can be more serious when it occurs.

— *Cosmetic disfigurement:* IH on the face or other visible areas can cause cosmetic concerns for both the child and the parents, as visible scarring or skin texture changes may remain.

— *Psychosocial impact:* Children with visible IHs may experience psychosocial challenges due to teasing or self-esteem issues. Parents may also experience emotional distress when dealing with their child's condition.

— *Strabismus:* IH near the eye can lead to strabismus (crossed eyes) if not managed appropriately.

— *Airway obstruction:* IHs in the throat, nose, or neck area can cause airway obstruction in severe cases. Prompt medical attention is crucial in such instances.

— *Hemorrhage:* Although rare, IHs can bleed spontaneously or following minor trauma. Bleeding can be concerning, especially in cases of ulceration.

It's important to note that most IHs do not lead to complications and tend to regress over time. However, any infant with an IH should be closely monitored by a healthcare provider to assess its growth and development.

To date, a very clear scheme of indications and contraindications for the treatment of IHs has been developed. While previously the «wait and see» method was considered expedient, today IHs are divided into groups depending on their risk (low, medium, high, the highest, etc.), which gives an understanding of which IHs need to be treated and how.

Today, β-blockers are the primary option for the treatment of IHs, which not only has significant effectiveness but also greatly simplifies the treatment of this pathology, making it possible to be performed not only by a qualified dermatologist but also by a pediatrician and even remotely by the method of telemedicine.

The use of β-blockers for the treatment of IHs was proposed by Dr. Christine Léauté–Labrèze and her colleagues in 2008 [19]. They conducted a study that demonstrated the efficacy of propranolol, a β-blocker, in treating IHs, leading to a significant breakthrough in the management of this condition.

β-blockers work by antagonizing the effects of adrenaline (epinephrine) and norepinephrine, two neurotransmitters that stimulate beta-adrenergic receptors in the body [14,20,30,41]. The mechanism of action of β-blockers can be summarized as follows: binding to beta-adrenergic receptors, inhibition of adrenergic stimulation, reduction of heart rate, lowering blood pressure, and bronchoconstriction. Also, β-blockers can have various effects on other organ systems, such as reducing the release of insulin from the pancreas, which can impact blood sugar levels. They may also affect the nervous system, reducing symptoms of anxiety and tremors.

Overall, the mechanism of action of β-blockers is to counter the effects of the sympathetic nervous system, which is responsible for the «fight or

flight» response. By blocking beta-adrenergic receptors, β-blockers help reduce heart rate, blood pressure, and the workload on the heart, making them valuable medications in the management of conditions like hypertension, arrhythmias, and anxiety and, in the case of IHs, for promoting the regression of these vascular growths. The determination of the method and its indications or contradictions before the start of treatment is one of the most important key points in the management program of patients with IH [16,39].

The purpose of this review was to familiarize the audience with the benefits of treatment with local β-blockers (it has almost no systemic side effects), to analyze the effectiveness and limitations of the use of topical β-blockers, to show the possibility and feasibility of managing IH in pediatric practice, and to demonstrate that its goal is not to treat complications, but to prevent them from occurring and to obtain an ideal medical and cosmetic effect.

We analyzed 18 literature reviews and clinical studies published in PubMed and MEDLINE during the 2012–2023 period, where the use of local β-blockers in IH was studied, including treatment carried out in dermatology and pediatric inpatient 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 (Table).

In general, we reviewed 18 articles (including reviews, meta-analyses, clinical trials, and cases) that involved about 3252 children (ages from birth until 15 months) with more than 3300 IH of different types (from small and superficial to extensive and complicated). We compared treatment with different β-blockers, their outcomes, and complications.

Table

The list of reviewed research about IH cases in children from birth to 15 months

Author, year, type of research	Number of patients, age	Diagnosis	Treatment	Outcomes	Complication
Y.J. Tang et al. (2015), clinical trial	33 children	Superficial IH	Topical propranolol gel for 1 and 3 months of use	The clinical efficacy of topical propranolol gel at 1 and 3 months of use was 45 and 82%, respectively.	None
A. Price et al. (2018), systematic review	597 patients with 632 IH	Small superficial hemangiomas at risk of cosmetic consequences	Three topical forms of propranolol: cream, ointment, and gel	90% of lesions improved from the start of treatment. A good or excellent response (at least 50% reduction in size) was observed in 59% of cases	Minor local reactions were observed in 1.3% of patients
G. Xu et al. (2012). clinical trial	25 children in the age range of1–10 months (28 lesions)	Superficial IH	1% propranolol cream	90% demonstrated a good (57%) or partial (33%) response to treatment	None
M. Kovačević et al. (2014), clinical trial	5 boys and 3 girls aged 3 to 12 months	Superficial IH on the forehead, back of the neck, forearm, abdomen, or back	1% propranolol cream	Archauer system. The majority of treated hemangiomas (62.5%) reached IV degree. The III-degree result was achieved in 12.5% and II degrees in 25% of patients with IH on the abdomen	None
Y.N. Zhai et al. (2013), clinical trial	51 children	IH	3% propranolol gel	Archauer system. Grade I (poor) reaction accounted for 17.24%, grade II (moderate) – 24.14%, grade III (good) – 44.83%, grade IV (excellent) – 13.79%	ND
J. Mashiah et al. (2017), retrospective study	63 patients with 75 IH	IH	4% propranolol gel	57.3% showed a good response, 25.3% – a partial response, and 17.3% – a poor or no response to treatment	Minor local side effects
L.Q. Gan et al. (2018), follow-up study	224 captives	Superficial IHs	2% drops of carteolol	24 had a good response, 162 had a partial remission, and 38 had no response	None
A. Chakkittakandiyil et al. (2012), retrospective review	73 patients	Most patients had superficial hemangiomas	Timolol maleate gel 0.1 or 0.5% (62/73)	>95% showed improvement as measured by visual analog scale (VAS)	ND

Continuation of table

Author, year, type of research	Number of patients, age	Diagnosis	Treatment	Outcomes	Complication
D.P. Xu et al. (2015), clinical trial	35 children, mean age 4.7 months	Superficial IH	Topical timolol maleate	51.4% had a good response, 31.4% had a partial response, and 17.2% had no response	None
F.Z. Muñoz–Garza et al. (2021), clinical trial	60 patients with IH in the first 2 months of life	Localized, segmental, or indeterminate IHs located on the head and/or neck or other body sites	0.5% timolol maleate solution	No significant differences were found between the timolol and placebo groups in terms of complete or near-complete resolution of IH at 24 weeks	ND
Z.Y. Ng et al. (2016), review of 4 articles	ND (Children up to 12 months of age)	Cutaneous IH on the face	Topical timolol as primary monotherapy	Achievement of clinically significant improvement (SAS) ranged from 47 to 88%	ND
K. Püttgen et al. (2016), retrospective study	731 patients	Localized (80.1%) and superficial (55.3%) IH	Topical timolol	Timolol is a well-tolerated, safe treatment option that demonstrates the best response in thin superficial IH regardless of pretreatment size	Side effects were mild and occurred in 3.4% of patients
S.A. Ovadia et al. (2015), meta-analysis of 17 studies	550 patients	Superficial hemangiomas	Topical β-blockers	The response rate to treatment was 80% for superficial hemangiomas.	ND
H.W. Wu et al. (2018)	362 / 362 patient	IH	Oral propranolol 2.0 mg/kg/day / topical timolol	Satisfactory therapeutic results in 97 / 96.4%, respectively. No significant differences between the two groups	Systemic adverse events with oral propranolol (3.9%) / with topical timolol (0%)
G. Li et al. (2016), clinical trial	31 patients	Mixed IH in the mouth and maxillofacial area	Oral propranolol and topical timolol maleate VS. propranolol	Combined use of oral propranolol and topical timolol maleate has a better clinical response than oral propranolol alone	None
L. Weibel et al. (2016), clinical trial	40 infants (age range 2–35 weeks)	Small proliferative hemangiomas	Topical timolol gel 0.5%	Hemangiomas improved significantly during treatment, with a median VAS increase of 7 points at 5 months. Local timolol therapy is effective in IH, but systemic absorption of timolol occurs	ND
M. Almebayadh (2020), clinical case	2 cases	Ulcerative IH	Cream with brimonidine 0.2% and timolol 0.5%	The ulcers healed within 7–10 days after treatment	None

Note: highlighted used in the trials' methods of treatment and their effectiveness, indications for their appointment, and complications; ND — no data.

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

Nowadays, the pathogenesis of IH is poorly understood, but several hypotheses have been put forward. Although none of them explain all the characteristics of IH, ongoing research into the pathophysiology has led to the development and implementation of new treatment options [22,33]. Thus, it was suggested that the renin-angiotensin system (RAS) may play a key role in the proliferation of endothelial cells in IH [11]. T. Itinteang et al. (2011) reported that IH endothelial cells in the proliferative phase express angiotensin-converting enzyme (ACE) and angiotensin II receptor (ATII), integral components of the renin-angiotensin system (RAS). The authors suppose that high levels of renin in blood serum, together with local expression of ACE, lead to a high concentration of ATII and stimulate IH cell proliferation [10]. In addition, recent studies have demonstrated increased RAS activity under conditions of hypoxia or oxidative stress [18] and, in particular, the role of hypoxia-inducible factor-1α (HIF-1α) and its targets, including the molecular marker GLUT-1 and vascular endothelial growth factor (VEGF), in the development of IH [13]. Also, spontaneous involution of IH may be associated with a sharp decrease in serum renin levels with age and/or depletion of endothelial progenitor cells over time [11].

The potential connection with the RAS can explain the mechanism of action of β-blockers, the use of which has become a real revolution in the treatment of IH [19,35]. In the world literature,

the strategy of prescribing the non-selective adreno-blocker propranolol for the treatment of IH is widely covered. Various explanations have been proposed for the mechanism of propranolol's effect on IH-producing cells, including its vasoconstrictor, antiangiogenic, and apoptotic effects [14,20,30,41]. It has been demonstrated that propranolol (at a dose of 2 mg/kg) is an effective drug at all stages of the development of IH, both to stop growth during the proliferation phase and to accelerate the involution phase [8,9].

β-blockers offer several benefits, but they can also be associated with potential side effects and complications. As has been shown in analyzed studies, β-blockers have shown remarkable efficacy in promoting the regression of IHs. They can lead to a significant reduction in the size and color of the IH. By reducing the size of the IH, β-blockers can help prevent complications associated with these growths, such as ulceration, functional impairment, and cosmetic disfigurement. Treating IHs with β-blockers can lead to an improved quality of life for both the child and their family, as it addresses the psychosocial impact and functional concerns. Propranolol and other β-blockers can help minimize scarring that may result from ulceration or healing of the IH.

Simultaneously, complications caused by the use of β-blockers can be determined from the literature and personal observations [12]. It is known that β-blockers can lower blood pressure and heart rate, which may lead to hypotension and bradycardia. They can affect glucose metabolism and potentially lead to hypoglycemia, particularly in young infants. In rare cases, β-blockers may cause respiratory distress and bronchospasm, especially in infants with pre-existing respiratory issues. Prolonged use of β-blockers can alter thyroid function, potentially leading to hypothyroidism. Nausea, vomiting, and diarrhea are possible gastrointestinal side effects.

It is important to note that these complications mainly concern the systemic use of the drug. Close monitoring during treatment is essential to minimize the risk of side effects and complications. Most side effects are temporary and can be managed with appropriate medical care.

Due to the risk of systemic side effects, the recommended topical administration of propranolol and the β1- and β2-adrenoceptor blocker timolol, which is safe and effective, has a minimal number of side effects, allowing the agents to be considered a primary treatment, especially in the early stages of the development of IH or with small, thin lesions [28]. Theoretically, topical β-blockers act only locally and do not enter the systemic circulation. But nowadays, local β-blockers are used to treat IH with both deep and superficial components of lesions, as well as amblyogenic IH [29].

As shown in Table 1, many studies are available on the use of topical propranolol. Y.J. Tang et al. (2015) investigated the effect of propranolol gel on the level of plasma renin, ATII, and VEGF in superficial IH (n=33). The control group consisted of 30 healthy infants of the same age. The clinical efficacy of topical propranolol gel at 1 and 3 months of use was 45% and 82%, respectively. The levels of renin, ATII, and VEGF in the blood plasma before treatment were higher than in the control. Concentrations of VEGF and renin after 1 and 3 months of treatment were significantly reduced compared to the values before treatment (271.51±18.59 vs. 362.16±27.29 and 405.18±42.52 vs. 565.86±49.66 pg/ml; 240.80±19.89 vs. 362.16±27.29 and 325.90±35.78 vs. 565.86±49.66 pg/ml, respectively), but ATII levels in plasma decreased slightly. It was concluded that since increased levels of renin, ATII, and VEGF are recognized as risk factors for the occurrence and development of IH, propranolol gel can inhibit the proliferation of IH by reducing the concentration of VEGF and renin [36].

A systematic review (12 articles, 597 patients with 632 IH), conducted by A. Price et al. (2018), evaluated the use of topical propranolol. Three topical forms of propranolol were used: cream, ointment, and gel. The concentration of propranolol ranged from 0.5 to 5%. The duration of treatment ranged from 2 weeks to 16.5 months. Overall, 90% of lesions improved after the start of treatment. A good or excellent response (at least 50% reduction in size) was observed in 59% of cases. Earlier initiation of treatment (under 3 months of age) was correlated with improved outcomes. No systemic side effects were reported. Minor local reactions were observed in 1.3% of patients. The authors believe that topical propranolol is safer than oral propranolol, although it may be less effective. Topical propranolol is more suitable for patients with small superficial IHs at risk of cosmetic consequences [31].

G. Xu et al. (2012) stated that therapy with 1% propranolol cream is a safe and effective treatment for superficial IH and can be used as an adjunctive treatment. 25 children in the age range of 1–10 months (28 lesions) were treated. Propranolol was applied topically three times

daily for 21 weeks (range: 5–59 weeks). Of the 28 IHs according to the 3-point system, 90% demonstrated a good (57%) or partial (33%) response to treatment. Systemic complications were not observed in any of the patients [40].

The clinical efficacy and safety profile of 1% propranolol cream for the treatment of superficial IH (n=33) were determined by M. Kovačević et al. (2014) Five boys and three girls aged 3 to 12 months with superficial IH on the forehead, and back of the neck, forearm, abdomen, or back were examined. Propranolol was administered twice daily for 10 months, with clinical evaluation every 1–2 months. Efficacy was assessed according to the Archauer system: grade I (poor): <25% reduction in size; grade II (moderate): 26 to 50% reduction; grade III (good): a reduction from 51 to 75%; and grade IV (excellent): >75% reduction. The majority of treated IHs (62.5%) reached the IV degree. The III-degree result was achieved in 12.5% and the II-degree in 25% of patients with IH on the abdomen. The treatment was well tolerated without side effects, i.e., topical application of 1% propranolol cream is a safe, effective, and inexpensive therapeutic option for the treatment of superficial IH [17].

Y.N. Zhai et al. (2013) treated 51 children with IH with 3% propranolol gel 3–4 times a day by evenly applying the gel to the lesion surface. The Archauer system was used to evaluate the therapeutic efficacy of topical propranolol over 1–10 months. Patients with a grade I (poor) reaction accounted for 17.24%, grade II (moderate) – 24.14%, grade III (good) — 44.83%, and grade IV (excellent) — 13.79% [42].

J. Mashiah et al. (2017) conducted a retrospective study of the results of topical treatment of 63 patients with 75 IH with 4% propranolol gel (150 mg/5 cm^2 per lesion, twice daily for 5–9 months). Of the total number of IHs, 57.3% showed a good response, 25.3% had a partial response, and 17.3% had a poor or no response to treatment; that is, 82.6% of cases recorded a good or partial response to treatment. Age at initiation of treatment, duration of treatment, thickness of the superficial component, and size of lesions have been shown to predict response to therapy. At the same time, minor local side effects were observed in only two patients: irritation, redness, and peeling of the treated area. No systemic side effects were reported [23].

L.Q. Gan et al. (2018) conducted a follow-up study of the results of the stagnation of carteolol for the treatment of superficial IHs. The study included 349 patients, who were divided into two groups: the treatment group (n=224) with 2% drops of carteolol hydrochloride two days per day for 6 months; and the caution group without treatment. Among infants treated with carteolol, 24 had a good response, 162 had partial remission, and 38 had no response. In the observation group, 7 cases had remission, 32 had partial remission, and 86 had no remission. No adverse reactions were observed, meaning that 2% carteolol hydrochloride drops are an effective and safe topical treatment for IH [7].

One of the first series of studies conducted by A. Chakkittakandiyil et al. (2012) retrospectively reviewed the results of treatment for 73 patients who received timolol maleate gel 0.1 or 0.5% (62/73). Most patients had superficial IHs, and >95% showed improvement as measured by the visual analog scale (VAS). Predictors of a better response were the superficial type of IH, 0.5% timolol concentration, and duration of use of more than 3 months [3].

H. Chan et al. (2013) found that timolol was more effective for lesions with a mean diameter <11.3 mm (100 mm^3 in volume) compared to larger lesions. It is recommended to use timolol maleate, 1 drop of gel, twice a day. One drop of timolol maleate (0.5%) contains 0.25 mg of the drug [4]. Some authors recommend using timolol maleate 3–4 times a day [27]. Treatment is more effective in the proliferative phase than in the involution phase, and plaques respond better to therapy than nodules [4].

D.P. Xu et al. (2015) evaluated the clinical effects and safety of topical timolol maleate every 12 hours for 22 weeks for the treatment of superficial IH (n=35, mean age 4.7 months). Changes in the size, texture, and color of the mass were recorded monthly. All patients completed the treatment. Of the 35 IHs, 51.4% had a good response, 31.4% had a partial response, and 17.2% had no response. The total response rate was 82.8%. No systemic or local side effects caused by timolol maleate were observed. The authors believe that topical timolol maleate may be an effective and safe alternative to systemic propranolol for the treatment of superficial IH [40].

F.Z. Muñoz–Garza et al. (2021) investigated the efficacy of 0.5% timolol maleate solution twice daily for 24 weeks for the treatment of IH in the first 2 months of life (n=60). IHs were localized, segmental, or indeterminate in 87, 10, and 3%

of patients, respectively, and were located on the head and/or neck (33%) or other body sites (67%). No significant differences were found between the timolol and placebo groups in terms of complete or near-complete resolution of IH at 24 weeks (42% vs. 36%). There were no differences in the reduction of IH size (volume and thickness). Color improvement was observed in week 4 in the timolol group. The results demonstrated that topical treatment of IH with timolol in the proliferative phase can prevent further growth and the need for treatment with oral propranolol [25].

In a review of four articles by Z.Y. Ng et al. (2016), they evaluated the results of topical timolol as primary monotherapy for cutaneous IH on the faces of children up to 12 months of age and determined differences in outcomes between early (before 6 months) and late (after 6 months) initiation of treatment. Achievement of clinically significant improvement, defined by a standardized assessment score of 3 or higher, ranged from 47% to 88%. IH regression was greater in patients who received timolol before 6 months of age than in patients who started treatment later [26].

Since the topical use of timolol in a large cohort of the pediatric population with IH is insufficiently covered, K. Püttgen et al. (2016) retrospectively evaluated timolol efficacy and safety, response-related characteristics, and adverse effects among 731 patients. The majority of IHs were localized (80.1%) and superficial (55.3%). Distortion risk was the most common indication for therapy (74.3%). Duration of therapy, initial thickness, and subtype were significant predictors of treatment response. The best response was observed with superficial IH <1 mm thick. 7.3% of patients needed further therapy with systemic β-blockers. Side effects were mild and occurred in 3.4% of patients. No cardiovascular side effects were documented. The authors concluded that timolol is a well-tolerated, safe treatment option that demonstrates the best response in thin superficial IH, regardless of pretreatment size. Timolol can be recommended as an alternative to systemic β-blockers, and watchful waiting for the involution of IH [32].

S.A. Ovadia et al. (2015) published a meta-analysis of 17 studies involving 550 patients evaluating topical β-blockers. The response rate to treatment was 80% for superficial IHs. A significant difference between local propranolol and timolol was not registered [28].

According to H.W. Wu et al. (2018), both oral propranolol (n=362) at 2.0 mg/kg/day and topical timolol (n=362) by applying three times a day a thin layer of hydrogel over the entire lesion surface for 6–7 months achieved satisfactory therapeutic results of 97% and 96.4%, respectively. No significant differences were found in the improvement of VAS scores between the two groups. The incidence of systemic adverse events in patients treated with oral propranolol (3.9%) was significantly higher than in patients treated with topical timolol (0%). Clinical response was not associated with sex, duration of treatment, location, size of lesion, or gestational age at birth, but was closely associated with age at the start of treatment, i.e., a younger age at the start of treatment predicted a higher rate of regression [38].

The combined treatment of mixed IH with the combined use of oral propranolol and topical timolol maleate is not well documented in the literature. In their study, G. Li et al. (2016) included 31 patients with mixed IH in the mouth and maxillofacial area who were divided into experimental (group A, n=14) and control (group B, n=17) groups. Group A patients received oral propranolol in combination with topical timolol maleate, and group B patients received propranolol alone. The maximum duration of treatment was planned for 8 months. There was a significant fading of color in group A (mean VAS score: 8.36±1.39) than in group B (7.18±1.71) at the end of treatment, while the reduction in size in group A (8.00±1.75) was not significantly different from group B (7.59±1.80). The duration of treatment in group A was shorter than the duration of treatment in group B (5.64±1.45 and 6.71±1.10 months, respectively). Therefore, the combined use of oral propranolol and topical timolol maleate contributes to a better clinical response in the treatment of mixed IH than oral propranolol alone. No serious side effects were observed in both groups [21].

It has not been definitively established whether topical β-blockers act only locally or whether their action is partially due to systemic absorption. L. Weibel et al. (2016) treated 40 infants (age range 2–35 weeks) with small proliferative IHs with topical timolol gel 0.5% twice daily and assessed urinary timolol excretion and serum levels. 23 patients (58%) had superficial IHs, and 17 (42% had mixed IHs. The average size of IH was 3 cm^2 (from 0.1 to 15 cm^2). IHs improved significantly during treatment, with a median VAS increase of 7 points at 5 months. Urinalysis was positive in 20 of 24 patients (83%). Three infants were also positive for serum timolol

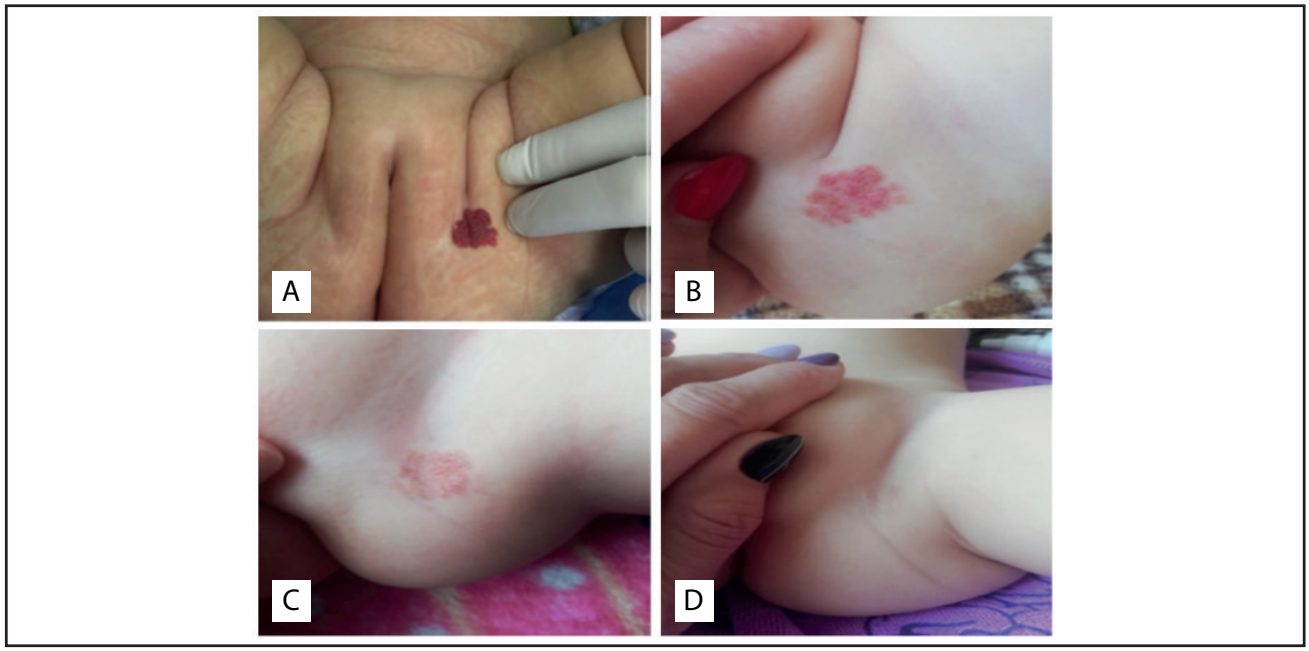

Fig. 1. Results of local treatment of IH with β-blocker timolol maleate gel 1%: A — 4-month-old child, B — 8-month-old child, C — 10-month-old child, and D — 14-month-old child

(median 0.16 ng/mL [range 0.1–0.18 ng/mL]). No significant side effects were recorded. According to the authors' conclusions, local timolol therapy is effective in IH, but systemic absorption of timolol occurs. Because serum levels were low, this confirms that the use of timolol for small IHs is safe, but caution is advised when treating ulcerative or large IHs, in very young children, or with concomitant systemic propranolol [37].

Ulcers are the most frequent complication of IH. M. Almebayadh (2020) reports two cases of ulcerative IH treated twice daily with a new form of cream with brimonidine 0.2% and timolol 0.5% (a combination of a selective β-2-adrenergic blocker and a non-selective β-blocker). In both cases, the ulcers healed within 7–10 days after treatment. No local or systemic side effects were recorded. The author believes that brimonidine 0.2%-timolol 0.5% cream is a promising alternative for the local treatment of ulcerative IHs [1].

In our practice, we have been using a group of β-blockers in various dosage forms for the treatment of IHs for more than 10 years and had the opportunity to compare the effect of an ointment with a concentration of the active substance with anaprilin from 1% to 5% and the effect of a timolol gel with a concentration of 0.25% to 1%. This allows us to clearly define the advantages and disadvantages of each treatment method. In particular, the ointment with anaprilin caused a bigger number of complications: it is non-sterile (it cannot be used for IHs with ulcers), and it is dangerous to use near the eyes, nose, and mouth. There were significantly fewer cases of adverse reactions to the gel with timolol. It was noticed that using the gel twice a day is usually not enough; it depends on the age of the child, the location of the lesion, and the need to wash the child. In general, the dosage and frequency of application of the gel depended on the age of the patient and the proliferating activity of IH and varied from three times a day to every three hours (depending on the location of the lesion in the diaper area). At the same time, there was a much higher efficiency of using 1% gel, compared with 0.5% — a faster stoppage of IH growth was observed.

In particular, we use a topical β-blocker in the form of a gel containing timolol maleate at concentrations of 0.25%, 0.5%, and 1%. This product is sterile, can be used for ulceration and the location of IHs near the eyes and on the mucous membranes is accurate in dosage and is safe for the child. Numerous clinical cases have proven its effectiveness. Below are some of them.

Clinical case 1

Patient: 1 year, 2 months (age 4 months at the beginning of treatment), female.

Localization: Skin of the genital area

Clinical diagnosis: IH in the proliferation phase.

The duration of treatment with a local β-blocker (timolol maleate gel 1%) was 10 months (Fig. 1 A, B, C, D).

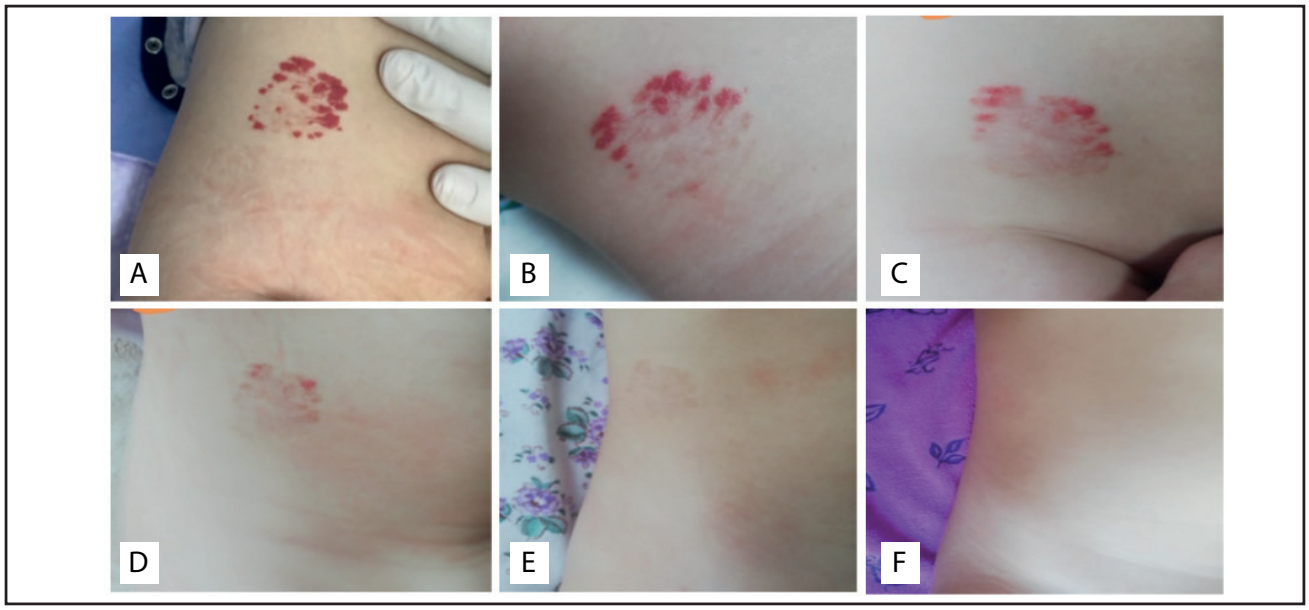

Fig. 2. Results of local treatment of IH with β-blocker timolol maleate gel 1%: A — 4-month-old child; B — 6-month-old child; C — 8-month-old child; D — 10-month-old child; E — 12-month-old child; F — 15-month-old child

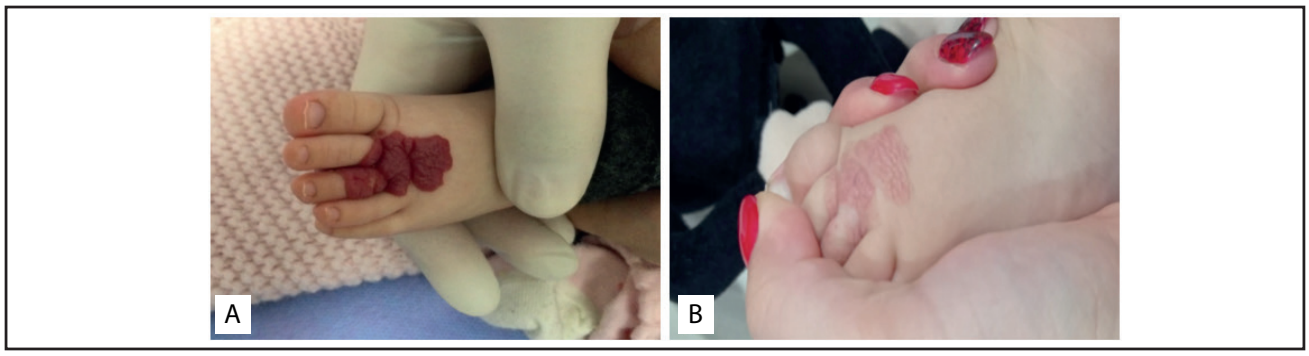

Fig. 3. Results of local treatment of IH with β-blocker timolol maleate gel 1%: A — 2-month-old child; B — an 11-month-old child

Clinical case 2

Patient: 1 year, 3 months (age 4 months at the start of treatment), female.

Localization: Skin of the lateral surface of the trunk.

Clinical diagnosis: IH in the proliferation phase.

The duration of treatment with local β-blocker timolol maleate gel 1% was 10 months (Fig. 2 A, B, C, D, E, F).

Clinical case 3

Patient: 11 months (at the time of treatment, age 2 months), female.

Localization: Skin of the foot.

Clinical diagnosis: IH in the phase of active proliferation with a tendency to exophytic growth.

The duration of treatment is 9 months (Fig. 3 A, B).

Clinical case 4

Patient: 1 year (age 1.5 months at the start of treatment), male.

Localization: Skin of the penis.

Diagnosis: IH in the phase of active proliferation.

Treatment: local β-blockers, timolol maleate gel 0.25–0.5% for 6 months of treatment (Fig. 4 A, B).

All treatment was carried out remotely.

Clinical case 5

Patient: 1,2 years (age 2 months at the start of treatment), male.

Localization: Skin of upper lip and nose.

Diagnosis: IH of critical localization in the phase of proliferation.

At the age of 2 months, treatment with timolol maleate gel 0.5–1%: was started after an in-person visit to the clinic.

Recommended: additional examination with the consultation of a cardiologist, ultrasound of the heart, and blood analysis to rule out contraindications of taking anaprilin. Anaprilin at a dose of 2–4 mg/kg for 12–15 months. During the additional examination time, apply local timolol maleate gel 0.5% for two weeks.

The result after two weeks of the timolol maleate gel 0.5% usage was so significant that there was no need to begin systemic anaprilin treatment.

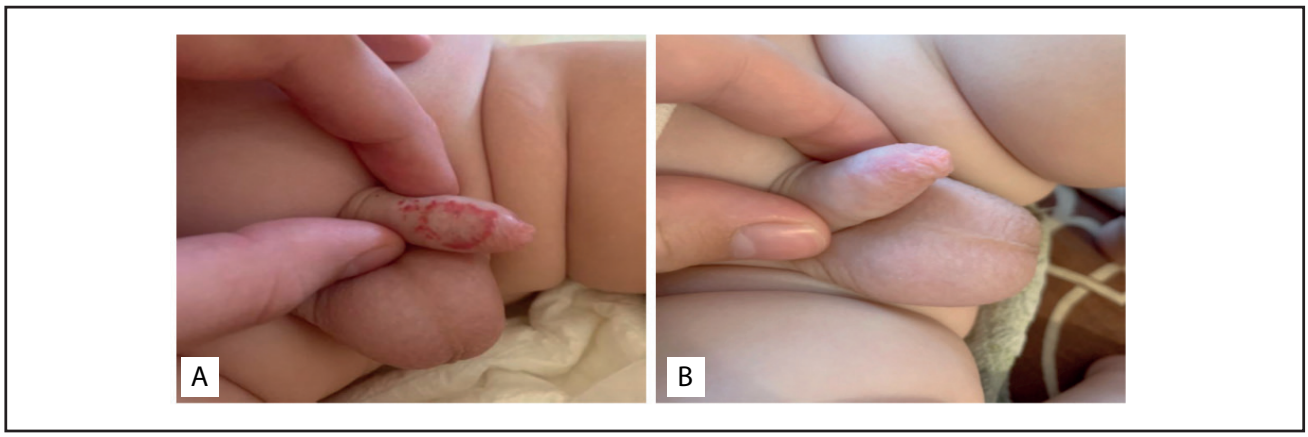

Fig. 4. Results of local treatment of IH with β-blocker timolol maleate gel 0.25–0.5%: A — 1,5-month-old child; B — 6-month-old child

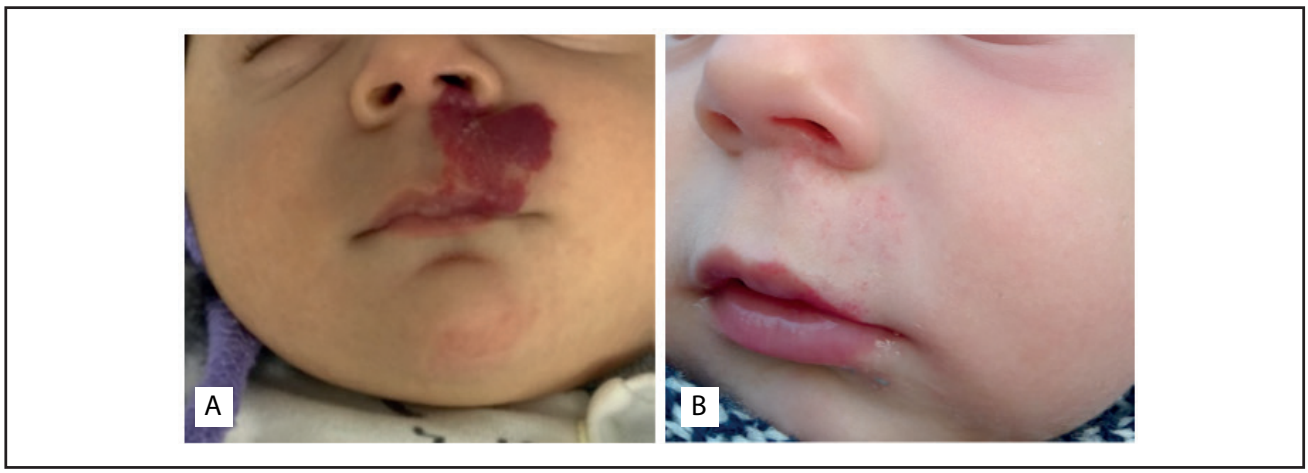

Fig. 5. Results of local treatment of IH with β-blocker timolol maleate gel 0.5–1%: A — 2-month-old child; B — 14-month-old child

Complete resolution of the IH was achieved within 12 months. Treatment with timolol maleate gel 0.5–1% — 12 months remotely, then patients came to the clinic for an ultrasound control to finish the treatment (Fig. 5 A, B).

Conclusions

Due to the accumulation of clinical studies and the analysis of their results, it is confirmed that β-blockers are the most modern, effective, and safe method of IH treatment, and can be used both for systemic and local use. Timely treatment initiation of local or systemic therapy allows to stop the proliferation of the tumor and prevent the development of complications and cosmetic defects, instead of treating them. Topical therapy with β-blockers is an effective and safe method of treatment for patients with different IH. In addition, such IHs may successfully be treated by doctors not of a dermatological profile, but by pediatricians or combined. Significant visual reduction in size has been reported in up to 80% of IHs. Treatment of complicated IHs involving deep soft tissues, mucous membranes, or airways usually requires comprehensive treatment (systemic propranolol, surgery, etc.), and the additional role of local β-blocker therapy and clear indications for its implementation are topics of future research.

It can be resumed that the use of topical β-blockers, such as timolol gel or solution, in the treatment of IHs offers several potential benefits:

1. Provide a non-invasive treatment option for IHs. This can be especially beneficial for parents and caregivers who prefer non-systemic treatments.
2. Topical application allows for a localized effect on the IH, minimizing systemic exposure and potential side effects associated with oral β-blockers.
3. Topical treatment can be initiated at an early stage when the IH is small, potentially preventing the need for more invasive treatments later on.
4. By promoting regression of the IH, topical β-blockers can help improve the cosmetic outcome, especially when used for superficial or facial IHs.
5. Topical application is associated with a lower risk of systemic side effects, such as hypotension or bradycardia, which can occur with oral β-blockers.

6. Topical treatments can be applied at home, which can be more convenient for parents and caregivers, and increase the possibility of being treated by pediatricians and dermatologists. In the case of natural disasters or military operations, the treatment can be remote via teledermatology.

7. The effectiveness of topical β-blockers depends mostly on the age at which treatment was started: the earlier the beginning — the higher the effectiveness.

8. Deeper or larger IHs may require systemic treatment with oral β-blockers or other interventions like laser therapy or surgical excision.

9. The choice of treatment should be individually selected according to the degree of risk of IH, its size, location, patient age and weight, and other parameters in each clinical case.

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