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MINIMALLY INVASIVE TREATMENT OF HEMANGIOMAS AT CHILDREN BY INJECTION OF TRIAMCINOLONE AND BETAMETASON

Resume. Introduction. In its development and course, hemangioma (HA) destroys and does not disperse surrounding tissues that causes significant functional and cosmetic damage. The widespread occurrence of HA in childhood, delayed diagnosis, unreasonable tactics, mistakes in the choice of treatment method, encourage specialists from a wide range of occupations to address constantly to this problem, which has not yet reached its final solving.

The use of traditional HA therapies often does not lead to the expected result, and is sometimes accompanied by complications of the tumor surface in the form of ulcers, which are accompanied by a long course of the inflammatory process and the lack of a tendency for rapid healing of ulcers.

Aim: to study the mechanism of action and effectiveness of triamcinolone and betamethasone in the injection method for the treatment of hemangiomas at children.

Materials and methods: the results of inpatient and outpatient treatment of 117 children (81 girls and 36 boys) with external HA localization. The material for the study was blood serum, in which, before the treatment on the 7, 14 and 21 days after intra-tumor injection of a mixture of triamcinolone and betamethasone the levels of acute phase inflammation proteins, namely sialic acids and seromucoids, were determined.

Results. Seromucoids level on the 7th day exceeded 4 times the value of the indicator before the beginning of treatment, respectively 0.72 ± 0.05 units of opt. density versus 0.18 ± 0.02 units of opt. density, ($p < 0.05$), on the 14th day exceeded the value 1.78 respectively 0.32 ± 0.04 units of opt. density versus 0.18 ± 0.02 of opt. density ($p < 0.05$), reaching almost normal level up to the 21st day. The level of sialic acids exceeded 1.76 times the rate before treatment, respectively, 3.52 ± 0.5 mmol / l versus 2.0 ± 0.3 mmol / l, ($p < 0.05$), on the 14th days only 1.16 times, respectively 2.31 ± 0.4 mmol / l against 2.0 ± 0.3 mmol / l, ($p > 0.05$), reaching a practically normal level up to the 21st day.

Taking into account the obtained dynamics of the proteins of the acute phase of inflammation, claimed that the maximum destructive effect on the HA tissue after the injection of triamcinolone and betamethasone occurs during the first 7 days, with a gradual decreasing in the expressiveness of the effective action to the 21st day.

Conclusions. Intra-tumor administration of triamcinolone and betamethasone contributes to satisfactory cosmetic and functional results at 95.73%, which allows it to be considered as an alternative to surgical excision of the tumor, in which technical difficulties and complications can occur.

Key words: children, hemangioma, triamcinolone, betamethasone, treatment.

Introduction. In its development and course, hemangioma (HA) destroys but does not disperse the surrounding tissues that cause significant functional and cosmetic damages, especially if localized in "critical zones". The widespread occurrence of HA at childhood, delayed diagnosis, unjustified expectancy

tactics, mistakes in choosing of the treatment method, encourages specialists from a wide range of occupations to address constantly this problem, which has not yet reached its final solving. Perhaps there is no child surgeon who would not treat HA in his practice, as there is no specialist who would not fail. [5]

Many authors have identified the high mitotic activity in the HA cells, and at the same time, the possibility of their "spontaneous" regression is marked, which fully corresponds to the tumor nature of the disease, although approximately 7-8% capillary HA are subject to involution, that located on the "closed" areas and only at full-term children over the age of 1 [1, 3].

In accordance with the recommendations of the international expert group WHO "Hemangiomas at childhood", the main spectrum of methods used in the treatment of HA is defined: laser therapy, cryodestruction, sclerosis HA with spirit, surgical excision [2, 4].

The use of traditional HA therapies often does not lead to the expected result, and is sometimes

accompanied by complications of the tumor surface in the form of ulcers, which are accompanied by a long course of the inflammatory process and the lack of a tendency for rapid healing of ulcers.

Methods of sclerotizing with alcohol go along with considerable duration, insufficient radicalization in rapidly growing HA, frequent complications that complicate the process of treatment.

Clinical example. Patient Sh., MCAP №9826, age 6, 8.08.2017, ask for medical help with complaints about the presence of tumor-like formation on the chin. From the anamnesis: sick from birth, at the age of 3 months, during a period of rapid increase HA tissue, in one of the CRP, 4 ml of 70% alcohol once was injected intra-tumoral (pic. 1).



Pic. 1. Patient Sh., MCAP №9826, age 6. General HA look after the alcoholinjection at the age of 3 months

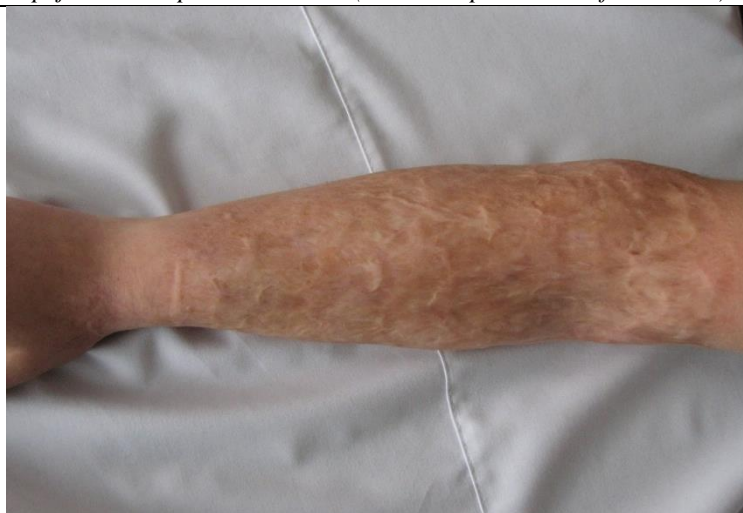
This treatment was ineffective. After the iterated examination, on August 9, 2017, HA was surgically removed. The postoperative period had a satisfactory period, recovery.

Radical excision of HA, especially on the open areas, is not always possible due to the risk of bleeding in the early postoperative period and the formation of cosmetic defects in the future. Not always the hormonal method is effective, which only inhibit the growth, contributing only to partial regression of the vascular tumor.

Cryodestruction, as a method of HA treatment, also has its numerous aesthetic and functional complications, in the form of colloid scars, incomplete tumor destruction, etc.

Clinical example. Girl I., 17 years old, MCAP №96, appealed to an outpatient reception to the Consultative Clinic VRNCH on January 19, 2017 with complaints about the presence of numerous scars on the right forearm. From anamnesis: a child is ill from birth, the diagnosis was - a cervical HA of the right forearm.

During the first year of the child's life, numerous (parents do not remember the number exactly) sessions of HA cryodestruction were conducted. During the examination in the area of the right forearm, along its front and lateral surfaces, numerous cheloid scars are observed. Some of the scars are prone to maceration, cracking and bleeding (pic. 2).

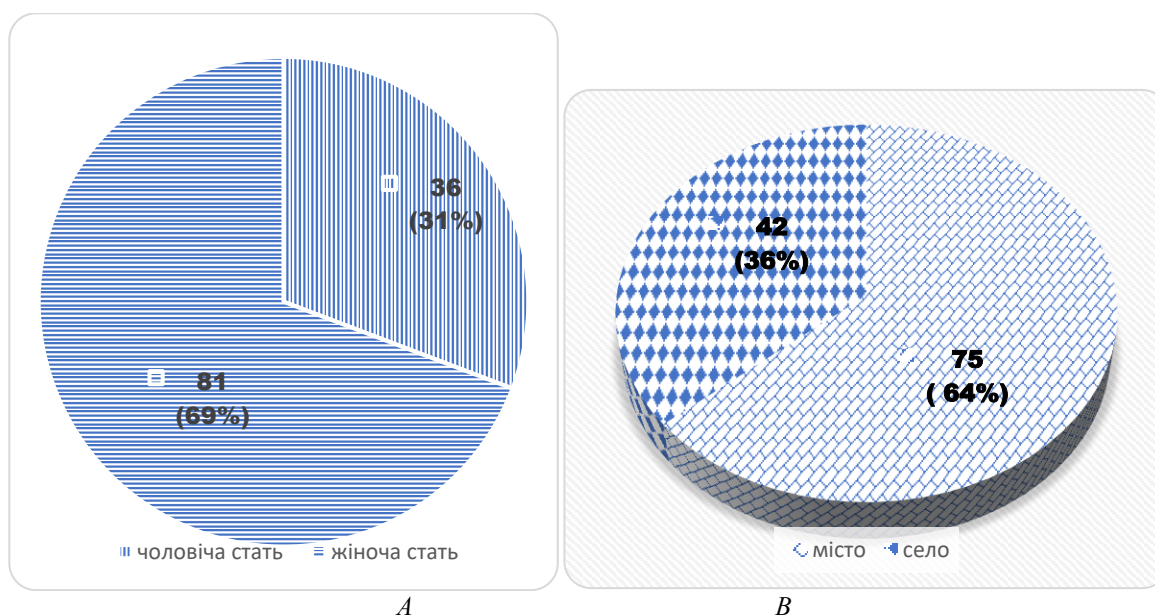


Pic. 2. Patient I., 17 years old, MCAP №96 Diagnosis: Multiple keloid scars of right forearm after cryodestruction of HA.

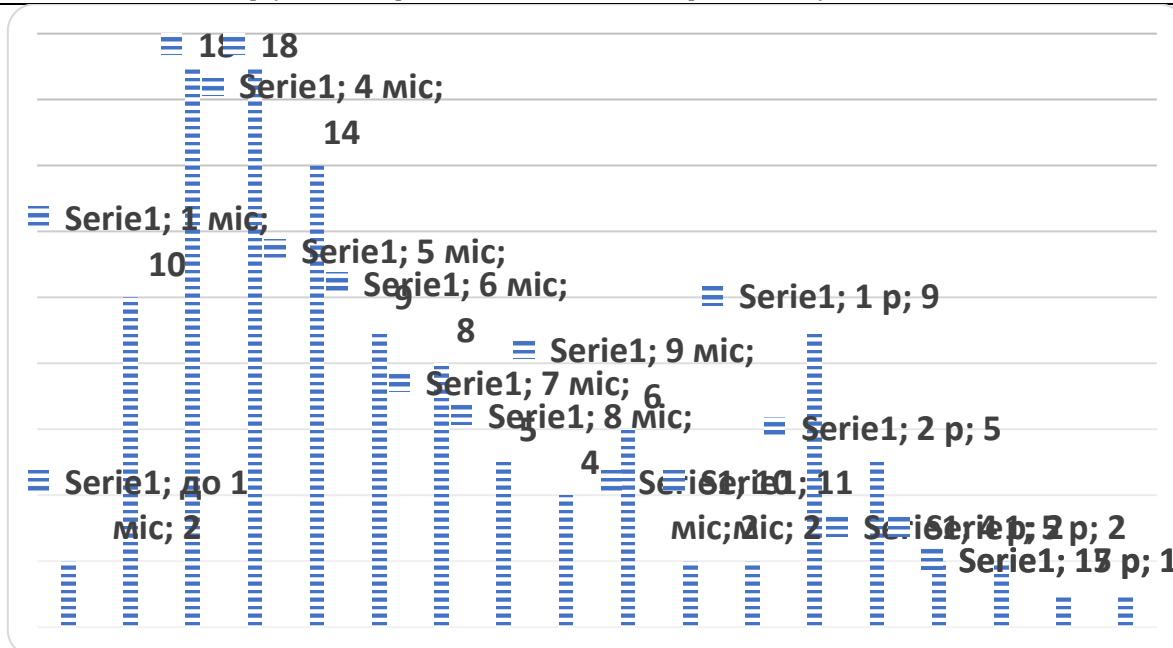
Aim of the work: to study the mechanism of action and effectiveness of triamcinolone and betamethasone in the injection method for the treatment of hemangiomas at children.

Materials and methods. The results of the in-patient and ambulatory treatment of 117 children (81

girls and 36 boys) with HA external localization were analyzed. 42 patients were rural residents, and 75 were urban (pic. 3). Distribution of patients by age is presented in Pic.4.



Pic. 3. Diagram of gender distribution of patients (A), and at the place of permanent residence (B).



Pic. 4. Diagram of patient distribution by age.

Blood serum was the material for the research, which was vacated in centralized delivery to a specialized biochemical laboratory. The selection of material for the research, considering the possible dynamics of acute phase proteins, was conducted at the beginning of the treatment, at 7, 14 and 21 days after intra-tumoral injection of a mixture of tritenolonone and betamethasone.

The determination of the concentration of sialic acids in the blood serum was conducted out by colorimetric method on a photoelectrocolorimeter in the mode of a green filter.

Determination of the level of seromucoids was carried out by the immunoturbidimetric method, in which the degree of dimness of the reaction solution determined the seromucoids contain in the blood serum in the range from 0 units S-H up to 15 units S-H (after Shank and Hoagland).

Results. In response to any damage (physical injury, burn, surgical manipulation, infection, growth and development of the tumor, the influence of chemical agents, etc.), a complex of physiological reactions aimed at the localization of the hearth of damage and recovery of disturbed functions is triggered. This process, aimed at restoring and preserving homeostasis, is widely known in the biological sense as inflammation, and the complex of local and systemic changes which occur directly from damage, in its totality, compose the concept of acute phase of inflammation (API), which is characterized by nonspecificity and versatility; the focus on limiting the center of damage, the implementation of reparative processes.

The development of API is initiated and regulated by cytokines, anaphylaxins and glucocorticoids, some of which are excreted directly in the inflammation center by activated macrophages, lymphocytes and other cells and which can provide both local and general effects. At the local reaction there is a change

in the lumen of the blood vessels, platelet aggregation with the formation of blood clots, accumulation of neutrophils and macrophages, the releasing of proteases and other lysosomal enzymes, the formation of kinins, prostaglandins and other mediators.

Usually the concentration of proteins API increases during the first 24-48 hours, and lasts within 7-10 days, which confirms the protective, homeostatic nature of this important answer. However, the normal course of API can be prolonged by continuation of the action of damaging factors or during the disorder of the control and regulation mechanisms.

HA refer to localized tumors with pathologic proliferation of endothelial cells, which is characterized by a phase of hypercellular growth and a prolonged involutional phase. Therefore, the first 12-16 months of a child's life are the most favorable in the application of minimally invasive treatments. In addition, the relative indication at the beginning of the treatment in older children, during the so-called phase of the involution, was a progressive increasing of the HA tissue or complete absence of a tendency to decreasing, the formation of ulcers, bleeding and inflammatory processes of infectious etiology.

As a minimally invasive method, we have used intra-tumour injection of a mixture of synthetic glucocorticosteroids, triamcinolone and synthetic corticosteroid betamethasone in age-related doses, in accordance with the instructions for the drugs using. The choice of triamcinolone and betamethasone was due to their ability to form a center of the local inflammation and antimetabolic properties to reduce the processes of neovascularization and proliferation.

A total of 117 patients had 152 HA centers, as 8 patients had the presence of several, from 2 to 8, tumor formations was determined. The total quantitative distribution of HA according to localization is given in Table. 1

The treatment session included intratumoral injectable administration of the mixture of triamcinolone + betamethasone in age-related dosages directly into the thickness of HA. The direction of administration of drugs with HA area of up to 15 cm² was selected from the periphery of the tumor to its center. The HA segment, on which the effect of the hormonal mixture is planned was chosen mainly in the projection of the existing feeding vessel, with the aim of a more significant therapeutic effect. Minimally invasive treatment by single administration of

triamcinolone and betamethasone was performed in 96 cases of HA of different localization.

Triamcinolone was used for one intramuscular injection at a rate of 1 - 1.5 mg / kg of mass, and betamethasone - 0.1 mg / kg. Depending on the area of the HA, its localization and depth of location, the dynamics of the development of inverse tissues tumor changes, the need for repeated treatment courses was calculated on a case-by-case basis. The interval between repeated doses of drugs was usually 6 - 8 weeks.

Table 1.

Quantitative distribution of HA according to localization.

Hemangiomas localization	Hemangiomas quantity	
	abs.	%
Scalp	23	15,13
Upper limb	20	13,16
Front abdominal wall	15	9,87
Back	14	9,21
Cheek	13	8,55
Chest	11	7,24
Lower limb	11	7,24
Forehead	9	5,92
Wrist	7	4,62
Nose	6	3,95
Breast	5	3,29
Sex organs and perineum	5	3,29
Upper lip	2	1,31
Lower lip	2	1,31
Neck	2	1,31
Foot	2	1,31
Upper eyelid	2	1,31
Lower eyelid	1	0,66
Chin	1	0,66
Hip	1	0,66
Total	152	100

In order to control the effectiveness of the minimally invasive treatment, the determination of the amount of intra-tumor injections of the triamcinolone and betamethasone mixture, except the visual

assessment, determined the planimetric tumor size and researched the dynamics of the level of markers of API (serumucoids and sialic acids) as an indicator of the destruction of the HA tissue (table 2).

Table 2.

Dynamics of API protein indicators after intra-tumor administration of triamcinolone and betamethasone

Indicator	Terms of serum blood test				
	Norm n=30	Before the treatment beginning n=30	7th day n=28	14th day n=25	21st day n=25
Seromucoids (un. Of optical density)	0.17±0.03	0.18±0.02	0.72±0.05*	0.32±0.04*	0.2±0.03
Sialic acids (mmol/l)	1.95±0.2	2.0±0.3	3.52±0.5*	2.31±0.4	2.08±0.3

*- p<0.05 in relation to the norm indication

The level of seromucoids on the 7th day exceeded the value of the indicator 4 times before the beginning of treatment, respectively 0.72 ± 0.05 units. of optical density versus 0.18 ± 0.02 units. of optical density, ($p < 0.05$), on 14th day in 1.78 times, respectively, 0.32 ± 0.04 units. of optical density versus 0.18 ± 0.02 units. of optical density, ($p < 0.05$), reaching practically normal level up to the 21st day. The level of sialic acids for the 7th day exceeded in 1.76 times the indicator rate

before treatment beginning, respectively, 3.52 ± 0.5 mmol / l versus 2.0 ± 0.3 mmol / l, ($p < 0.05$), on the 14th day only in 1.16 times, respectively 2.31 ± 0.4 mmol / l against 2.0 ± 0.3 mmol / l, ($p > 0.05$), reaching a practically normal level up to the 21st day.

Taking into account the obtained dynamics of API proteins, it's possible to affirm that the maximum destructive effect on HA tissue after the injection of triamcinolone and betamethasone occurs during the

first 7 days, with a gradual decreasing in the expressiveness of effective action to the 21st day.

Minimally invasive treatment was offered as a method to different HA areas. For one injection, the area of active healing exposure was up to 5.0-10.0 cm². The number of intramatural injections of triamcinolone and betamethasone was determined individually, in each particular case, calculated according to linear parameters (area, height, depth of distribution, expressiveness of the feeding vessels, etc.) and tumor growth rate, with the necessity of taking into account the effectiveness evaluation of the previous sessions.

A satisfactory result from treatment was observed at 112 (95.73%) patients, but at 12 (10.26%) patients, after 3-4 times injections, hypopigmentation of the skin was observed, and at 32 (27.35%) cases the atrophy of the subcutaneously- fatty tissue, which was fully recovered within 10-12 months after the end of the

treatment. With the complete further disappearance of HA tissue, the skin gradually acquires its usual appearance and structure, with a restored developed epithelial layer and sometimes with rests of the set of tiny vessels in the thickness of the dermis.

Clinical example. Girl B., MCAP №1385, 2 years old., 3.2.2015., was hospitalized to the pediatric surgical in-patients department with a diagnosis: cavernous hemangiomas of the nose to the left. From the anamnesis it is known that the child is ill from the moment of birth. Previously, asked to the district doctor for help, an expectation tactic was chosen. In the dynamics of monitoring of HA without a tendency to decrease, and during the last 2 months, mother admitted the tendency of increasing in the size of forming, around which a clear network of subcutaneous blood vessels began to be noticed (Pic. 6).



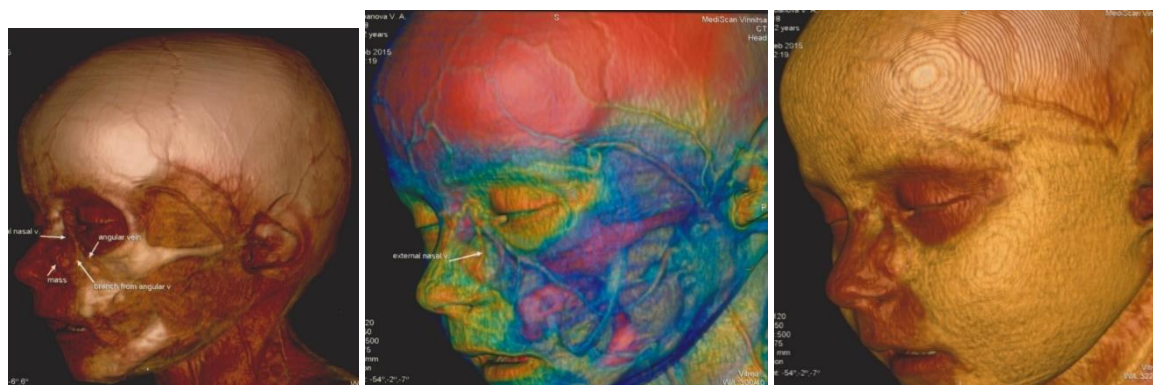
Pic. 6. Patient B., MCAP №1385, 2 years old., diagnosis: cavernous hemangiomas of the nose to the left. General appearance 3.2.2015.

During palpation on the area of the nose to the left with the transition to the left of the cheek, a tumor similar formation of mild-elastic consistency is determined; painless, with a total diameter of 4.0 cm. The ramified set of convoluted dark blue and red blood vessels is marked in the thickness of the skin above the formation. During pressing, the size of the HA is temporarily reduced due to its flattening.

Ultrasound of the formation: in the area the left ventricular lobe elevates the echogenicity of the

formation with an uneven unclear contour of 27×7.3 mm, the blood flow is intensified.

6.2.2015 CT scan of the head with an intravenous X-ray contrast enhancement was conducted, in which in the area of the left wing of the nose, with the transition to the left cheek, tumor formation was determined up to 3.2 cm², which in its structure resembles cavernous hemangiomas with feeding vessels (Pic. 7).



Pic. 7. Patient B., MCAP №1385, 2 years old., diagnosis: cavernous hemangiomas of the nose to the left. CST of the head with X-ray contrast enhancement, scans in 3D reconstruction.

The mixture of triamcinolone and betamethasone was intramuscularly injected twice with an interval of 3 months. Further, every 3 months, steady positive dynamics was observed in control surveys in the form

of a decreasing in the HA size. During examination of the patient at the age of 4 years, no tumor signs were observed, only certain subcutaneous vessels were observed (Pic. 8).



Pic. 8. Patient B., 4 years old. General appearance during the control examination (may 2017).

At the control ultrasound investigation of the back of the nose to the left in the gray-scale mode at a frequency of 11 MHz, voluminous formations of a

pathological nature were not found. In the color Doppler mapping mode, the blood flow locus is not defined in the specified area (pic. 9).



Pic. 9. Patient B., 4 years old. Ultrasound the back of the nose investigation in the color Doppler mapping mode (May, 2017).

At 56 HA, the area of which exceeded 15.0 cm², and the treatment of which required several sessions of injection, the latter began to be conducted from the periphery to the center, necessarily focusing on the localization of feeding vessels. The interval between

injections sessions ranged from two weeks to three months, was determined in each case, depending on the dynamics of the reverse development of HA. The quantitative distribution of multiplicity of injection sessions in this group of patients is given in table 3.

Table 3.

Quantitative distribution of injection sessions with HA in an area of more than 15 sm²

Multiplicity of injection sessions	Number of clinical cases (n=56)
2	28
3	17
4	6
5	5

Clinical example. Child D., MCAP №5320, 3 years and 9 months, came for a control examination for the treatment of HA forearm. From anamnesis: at the age of 4 months, on May 5, 2006, the child was given intramatural injection of TC and BM HA in the projection of its feeding vessels, which location was determined by ultrasound. On July 21, 2006, it was determined that there is no further growth of the tumor, the tissue of the HA decreased in volume, especially in height in its distal sections. The re-session of intra-

tumor injection of TC and BM was conducted age-related dose in the proximal tumor area in the vessels projections, that feed HA. In the process of the following control examinations, the positive dynamic was marked. 07.07.2013 during the control examination HA tissue is absent. Insignificant set of the thin blood vessels is seen in the recovered skin of the forearm. Lim function isn't disturbed (pic 10).



A



B



C



D



E



F



Pic. 10. Child D., MCAP №5320. Reverse developmental HA dynamics of the left forearm: A – the first TC and BM injection 5.05.2006; B – general appearance of HA before the second session of TC and BM injection 21.07.2006; C – general appearance of the forearm 2.03.2007; D- general appearance of the forearm 6.04.2007; E - general appearance of the forearm 8.06.2007; F - general appearance of the forearm 6.03.2009; G - general appearance of the forearm 18.09.2009; H - general appearance of the forearm 16.04.2010; I - general appearance of the forearm 28.11.2012.

Among 117 children who used single intra-tumor administration of triamcinolone and betamethasone, 4 patients (localization of hemangiomas in 2 cases - posterior neck area, 1 - left chest wall, 1 - anterior abdominal wall) treatment was used with the aim to eliminate HA relapses after their previous cryodestruction in the period of newborn birth and early (up to 3 months) age.

Clinical example. Child K., age of 8 months., MCAP № 9154. 2.6.2011, during an outpatient examination, mother complaints of relapse of the HA in the area of the posterior surface of the neck. From

the anamnesis: in the words of the mother, the girl is ill from the early age when HA was detected on the back of the neck ø up to 2.0 sm, which was prone to rapid growth. At the age of 1.5 and 4 months, the child was given two cryodestruction sessions that did not lead to complete destruction of the tumor. During examination, on the back of the neck to the right similar formation is defined as a tumor, that protrudes above the surface of the skin to 6 mm, with a rough scar. Under the thin skin there are elements of a cyanotic color of HA tissue, which, when pressed, diminish in size (Pic. 11 A).



A

B

Pic. 11. Child K., MCAP № 9154, diagnosis: HA relapse of the posterior surface after cryodestruction. General appearance: A - before treatment (age 8 months); B - after treatment (age 1 year)

Triamcinolone and betamethasone are injected in the age-related dose intra-tumor in the direction from the periphery to the center. At the age of 1, during palpation of HA tissue is not determined, the scar is diminished in size, tender; there are small remnants of intradermal vessels in the form of a weakly branched set in the upper part of the area of therapeutic effect (Pic. 11B).

Conclusions. Thus, conducted researches have shown that intratumor administration of a mixture of synthetic glucocorticosteroids triamcinolone and synthetic corticosteroid betamethasone causes the breakdown of tumor proteins, which is accompanied by an increasing in levels of seromucoids and sialic acids during the first week, which may indicate the presence of localized inflammation induced by this as a result of the destructuring of the HA tissue, and the determination of their level can serve as an indicator of the activity of such inflammation.

Intra-tumor administration of triamcinolone and betamethasone promotes maximal increasing of proteins of acute phase of inflammation up to 7 days of treatment: the level of seromucoids exceeded the value of the indicator four times before the beginning of treatment (0.72 ± 0.05 units of opt. density versus 0.18 ± 0.02 units of opt. density, respectively, $p < 0.05$), the level of sialic acids exceeded the value of 1.76 before the beginning of treatment (3.52 ± 0.5 mmol / l versus 2.0 ± 0.3 mmol / l, respectively, $p < 0.05$), indicating the

presence of the intensive destructive effect of HA tissue, which contributes to satisfactory cosmetic and functional results at 95.73%, and allows it to be considered as an alternative to surgical excision of the tumor, in which technical difficulties appear due to the difficulty of removing diffuse and non-encapsulated tumors without the risk of damage of surrounding tissues and the occurrence of bleeding.

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