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Intra-Lesional Injection of Anti-VEGF in the Management of Childhood Palpebral Hemangioma.

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Abstract: *Infantile hemangiomas (HI) are the most common benign vascular tumors in infants. The risk factors are currently well known and the pathophysiology is beginning to become clearer little by little thanks to recent studies concerning the clinical behavior and the triggers of HI. The diagnosis of hemangioma is essentially clinical, however additional assessments may be reveal to be necessary in front of certain forms of HI, in particular in front of a large segmental HI. Currently, systemic beta-blockers, and in particular propranolol, are the first-line treatment for HIs who are complicated or at risk of complications. However, intralesional injections of bevacizumab seem to be an interesting alternative with regard to uncomplicated skin HI. We were able to demonstrate through our study, remarkable efficiency. These results are generally comparable to the scant data in the literature. In addition to its effectiveness, these injections have several advantages. The most significant being the very minimal risk of side effects. Finally, it will of course be necessary for larger randomized studies to be carried out to confirm this very favorable benefit / risk report and allow obtaining a possible marketing authorization (marketing authorization). On the other hand, it will also be necessary to carry out studies with a longer follow-up in order to determine any possible complications, in particular systemic, of the drug used locally.*

Keywords: *palpebral hemangioma, child, Bevacizumab.*

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I. Introduction

Eyelid hemangiomas are the most common benign vascular tumors in infants. Infantile hemangiomas are benign tumors of the vascular endothelium. Because of their spontaneous involution, most palpebral hemangiomas (HI) do not require therapeutic intervention and simple monitoring is generally sufficient. in some cases, treatment is necessary, given the risk of complications (ptosis, restrictions of eye movements, and especially amblyopia) in addition to the aesthetic damage they can cause. Studies have confirmed the importance of the vascular endothelial growth factor (VEGF) pathway in HI and that it is a major stimulus responsible for cell proliferation and angiogenesis [1].

Bevacizumab is a fully recombinant humanized monoclonal antibody that binds to all vascular endothelial systems. Isoform of growth factor A (VEGF-A). Intravitreal Bevacizumab, alone or in combination, has been described in the treatment of capillary retinal hemangioma, where overexpression of VEGF is also observed [2].

In addition, its effectiveness has also been reported in the treatment of choroidal hemangiomas by intravitreal administration [3]. Based on these successful observations, the local use of anti-VEGF treatment in capillary hemangiomas of the eyelids could be a promising treatment.

The aim of our work is to evaluate the effect of anti-VEGF on eyelid HI compared to a control group through a series of cases followed in ophthalmology consultation at the ophthalmology department B at the specialty hospital Rabat between January 2019 and September 2019. The importance of our work is to present a potentially promising drug for a common but sometimes debilitating disease in early childhood and can encourage clinical researchers, especially those who have access to this drug, to conduct additional trials on this subject.

II. Methods

We conducted a prospective longitudinal study of 10 patients who consulted for an infantile palpebral hemangioma in ophthalmology consultation at the hospital des spécialités de Rabat between January 2019 and September 2019. Five patients received 3 injections of anti-VEGF (BEVACIZUMAB) which was started after favorable agreement from their parents. This had interested children with complicated eyelid HI. Only one case required prior surgical excision and intra-lesional injection following a recurrence.

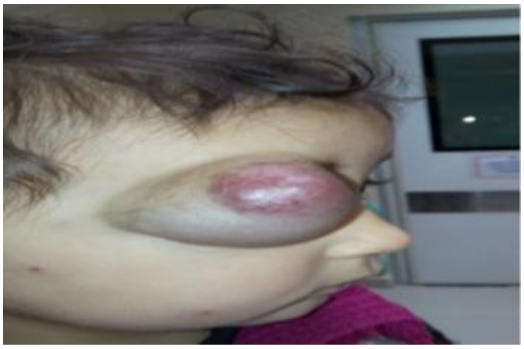
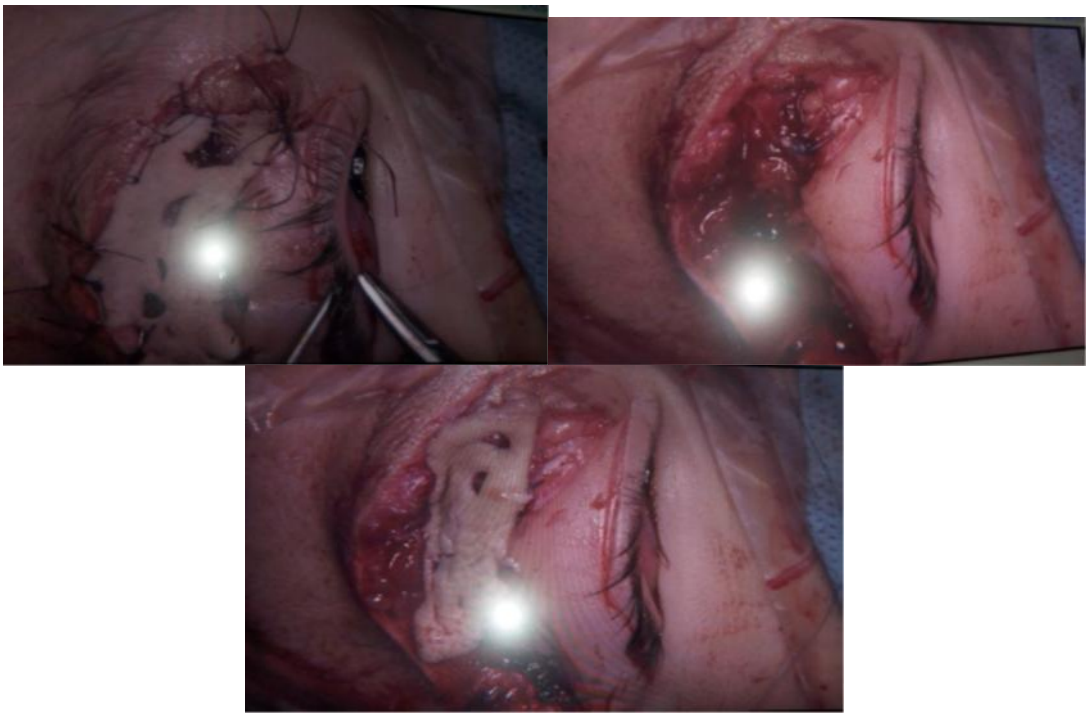


Figure 1: Profile view of the palpebral hemangioma - HSR Ophthalmologie B.

Figure 2 and 3 : The surgery consisted of a wide excision with scraping of the deep plane combined with a biopsy of the pieces measuring between 1.3 x 0.7cm and 1x 0.5cm with a greyish white appearance. Then we took a graft sample from the inner side of the right thigh. HSR – Ophthalmologie B



Figures 4,5 and 6: Images showing the placement of the skin graft. After a careful scraping of the graft in order to make it very fine, we perforated it and applied to the site of the excision. HSR - Ophthalmologie B

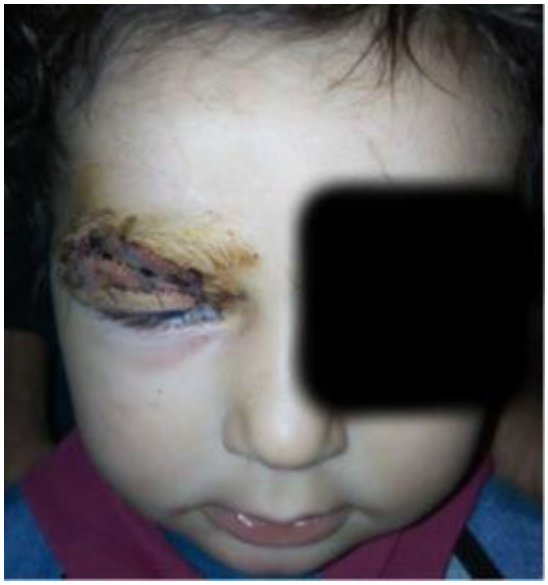


Figure 7: day 1 post surgery. HSR -Ophtalmologie B

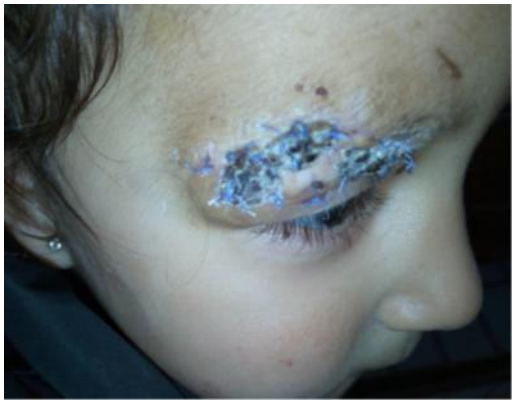


Figure 8: 1 month after surgery.HSR-Ophtalmologie B

Inclusion criteria: In the study were therefore included, patients who had had a previous treatment as well as patients who had a contraindication to oral beta-blockers, or even patients in whom oral therapy could not be established due to monitoring difficulties. No age limit has been set.

the duration of the treatment was fixed in advance at 3 injections spaced one month apart, the treatment was maintained as long as it was well tolerated and effective on the HI. Bevacizumab was administered by intra-lesional injection at a dose of 1.25 mg in 0.05 mL, followed by a light massage. The other 5 patients, whose parents did not accept the start of treatment with Bevacizumab, remained under simple medical supervision. The patients were followed-up regularly in consultation once every month and this even after stopping treatment for the group treated with Bevacizumab. At each consultation, a clinical examination was performed, a photo of the hemangioma was taken and filed by the same assessor, and side effects were sought. The primary endpoint was changing the size and extent of the HI red color by comparing each photo with the previous one. The main measure of effectiveness was regression of lesions by 50% and more compared to their initial sizes. The regression percentage was calculated by the following formula: Initial size-final size in% on the initial size. Information of interest was collected from each patient's medical record and photographs and / or imaging. The demographic and clinical data collected in the medical file of each child concerned: The demographic characteristics of the child, Any complications during pregnancy (targeting the complications that may be the cause of antenatal or perinatal hypoxia), The term of pregnancy, mode of delivery, height / weight / head circumference at birth, possible history of fetal distress at birth, possible transition to intensive care unit after birth, medical and surgical history of the child and significant family medical history. The data analysis was descriptive and bivariate. Qualitative variables were described by their frequencies and percentages, quantitative variables by measures of central tendency and measures of dispersion. The percentage comparison used the chi-square test, with a statistical significance threshold fixed at 5%. The therapeutic effectiveness was objectified by: Healing of the HI, disappearance of the crusts / improvement of the ulceration (partial healing), improved but persistent crusts / No improvement of the ulceration or the crusty state. Qualification of the color of the HI

for the surface component of the HI (bright red / tarnished red / pink / telangiectasias / no visible surface component) and for the deep component (sustained bluish halo / moderate to weak bluish halo / none visible deep component). The kinetics of growth of the HI: significant decrease in volume / decrease in mediocre volume / stable volume / increase in mediocre volume / significant increase in volume.

Tolerance to the treatment was apprehended by the collection of observed side effects and possibly attributable to systemic propranolol. With regard to the control of the regression of the HI we based ourselves on the echo-doppler realized in all the patients having received 3 injections of bevacizumab.

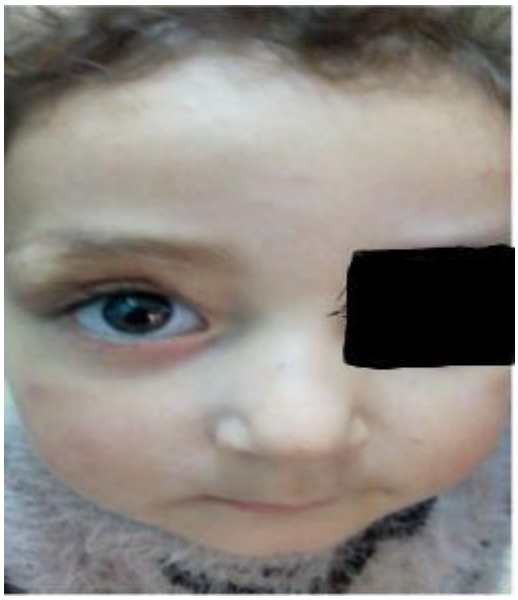


Figure 9 : Image showing the evolution after surgery and 3 anti-VEGF injections: Regression of more than 80% of the lesion. HSR - Ophthalmologie B.

Figure 10 and 11: The left image shows a hemangioma of the lower eyelid after 15 days of the first injection of bevacizumab, and right image of the lesion after 3 injections of anti-VEGF. HSR - ophthalmologie B

Figure 12 and 13 : Image on the left after the first anti-VEGF injection and on the right after the 3rd anti-VEGF injection. HSR - Ophthalmologie B.

III. Results

We selected 10 patients with eyelid HI, five of whom received intralesional BEVACIZUMAB (group 1) and five who received no treatment (group 2). Table I shows the epidemiological and clinical results of the two groups. The median gestational age [min -max] was 39.5 weeks. The average age of group 1 patients is 15 months with extremes between 6 months and 2 years. The average age of patients in the control group 2 is 24 months with extremes of 3 months and 4 years. The median birth weight [min -max] was 2950g [2000-3900] in the anti VEGF group against 2030g [2060 –4000] for group 2. A total of 3 pregnancies (60%) were of normal course in group 1, the other 2 pregnancies (40%) were complicated by 1 harmonious idiopathic intrauterine growth retardation (IUGR) in 1 case, and 1 well-followed gestational diabetes, compared with 5 normal pregnancies in group 2. To our knowledge, there was no context of perinatal hypoxia or family history of HI in the 2 groups. Childbirth was performed vaginally for 4 patients (80%) and by cesarean section for a patient (20%) in group 1 versus 5 vaginal deliveries in group 2. No patient required neonatal resuscitation, 1 child (40%) had presented with neonatal bronchiolitis in group 1 against 2 in group 2 and one case having progressed to asthma in group 1. In group 1, only one patient had another hemangioma located on the forehead Concerning patients in group 2, 1 patient had 2 other locations: face and scalp. 1 patient only had 2 other treatments before the introduction of bevacizumab (corticosteroid therapy then surgery), and 2 others had received local corticosteroid therapy without results. Bevacizumab was injected intra-lesion at a dose of 1.25 mg in group 1 every month for 3 months.A good evolution was noted in our patients with a regression in the size of half of the HI and a disappearance of the redness from the first weeks of treatment. The colorimetric variations were the first signs of therapeutic response observed in group 1, so all of our patients presented a change in the coloring of their hemangioma, which appeared on the first injection. In our series, the patients gradually regressed the volume of their hemangioma, with the exception of 2 cases, male infants who did not experience a volume regression after the first injection. No treatment-related adverse events were identified during the clinical examination or reported by the parents. After stopping treatment: No rebound effect was found after stopping treatment (1 month later).We studied the evolution of lesions in the two groups after an average of 2 months of follow-up. In group 1, a regression of HI was noted in 3 patients, a steady state was noted in the 2 other patients. In addition, in group 2, no patient experienced regression of the lesions, a steady state was found in only 1 patient and a slowly progressive increase in 4 patients. In total, improvement was objectified in 3 patients (60%) in group 1. On the other hand, there was no improvement in group 2. This difference was statistically very significant (p <0, 0001).

TABLE I

caracteristics	Group 1	Group2
Average age	14 months	24 monhs
Sex -female -male	 70% 30%	 83.3% 16.6%
Ratio	2.3	5
Antecedent: -neonatal suffering -prematurity -intrauterine growth retardation	 0 0 1	 0 0 0

-Gestational Diabetes **-asthma** **-bronchiolitis**	 **1** **0** **1**	**0** **1** **2**
Other location: **-face** **-torso** **-scalp** **-limbs**	 **0** **0** **1** **0**	 **1** **0** **1** **0**
Size	**0.5 to 6 cm**	**0.3 to 4.2 cm**
Good évolution	**60%**	**20%**

The Doppler ultrasound showed a reduction in lesion size of almost 50% in 3 out of 5 patients in group 1.

IV. Discussion

Infantile hemangioma (HI) is the most common benign childhood vascular tumor affecting 5-10% of infants and 30% of premature babies under 1500g. The results of our study, showing an average age of 15 months for group 1 and 24 months for group 2, are close to those of the Chilean series [4] having reported an average age of 9.7 months and l study by El Mouden [5], which was carried out in Marrakech, and which showed an average age of 9.4 months in a series of 46 patients. In most series, the median age varies between 3 and 6 months, especially in the multicenter study by Chakkittakandiyil [6] who found an average age of 3 months ± 3 weeks. HI corresponds to an abnormal proliferation of endothelial cells with an aberrant architecture of blood vessels. HI develops by proliferation of endothelial cells (strongly positive expression of MIB1, proliferation marker expressed by endothelial and interstitial cells) stimulated by the proangiogenic factors bFGF and VEGF (these are found in situ but also in blood and infant urine). Overexpression of angiogenic growth factors, including vascular endothelial growth factor (VEGF), has been demonstrated in capillary hemangiomas [7,8]. Palpebral hemangioma can be difficult to remove surgically, especially if it is significant. Treatment can be sought for reasons unrelated to regression, physical and functional comfort, or to prevent accidental trauma and bleeding. Bevacizumab is a fully recombinant humanized monoclonal antibody that binds to all isoforms of vascular endothelial growth factor (VEGF-A). Intravitreal bevacizumab, alone or in combination, has been described in the treatment of retinal capillary hemangioma, where overexpression of VEGF is also observed [9,10]. In addition, its effectiveness has also been reported in the treatment of choroidal hemangiomas by intravitreal administration.

Furthermore, it has been used in the treatment of retinal juxta-papillary capillary hemangiomas in the context of von hippel lindeau disease with very satisfactory results, some publications report encouraging results based on IVT of anti-VEGF, used alone or in combination with PDT, these studies again encouraged by the pathophysiology of these hemangiomas and the essential role of VEGF in their evolution [11-12].

However, they insist on the often transient nature of the effect of these treatments and on the need to have to repeat them in addition to prolonged monitoring [10,11,12]. Based on these successful observations, the local use of anti-VEGF therapy in eyelid hemangiomas is potential. A favorable response to treatment was observed in a pregnant patient who received 4 injections of bevacizumab for a lobular capillary hemangioma with a decrease in size exceeding half of the initial size [13]. To our knowledge, the first case of use of bevacizumab in cutaneous hemangioma was reported in 2012 by the team Laura L et al. The intralesional anti-VEGF treatment of capillary hemangioma presents a potential alternative as an adjunct to surgery or as an alternative treatment for the treatment of non-resolving lesions. The regression of the demonstrated vascular tissue can potentially reduce the tendency to bleed, thereby facilitating surgical resection. Anti-VEGF treatment could even be considered in various forms of periorbital or orbital capillary hemangioma, such as infantile lesions, in particular when systemic treatment, such as propranolol, is not suitable. [13] In addition, bevacizumab was compared in the study by Hanane et al to the injection of triamcinolone TAC. The result ruled that they were both safe and effective treatments for early proliferative HI after three sessions with equal results. However, ACT injection was significantly better and better than bevacizumab after six sessions. [14] Our study is lacking in hindsight but has shown satisfactory effects in our patients. The importance of our work is to introduce a potentially promising drug which has demonstrated its effectiveness in many fields against a common but sometimes debilitating disease during early childhood and which can possibly lead to amblyopia. this should therefore encourage clinical researchers, in especially those who have access to this drug, to continue the trials on this subject with a possible greater perspective. Additional research on the use of anti-VEGF therapy in capillary hemangiomas is likely to be necessary.

V. Conclusion:

It will of course be necessary for larger randomized studies to be carried out to confirm this very favorable benefit / risk report and allow obtaining a possible marketing authorization (marketing authorization). On the other hand, it will also be necessary to carry out studies with a longer follow-up in order to determine any possible complications, in particular systemic, of the drug used locally.

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