ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 10, pp.7541-7543, October, 2019

DOI: https://doi.org/10.24941/ijcr.36555.10.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

THE PROPRANOLOL AND INFANTILE HEMANGIOMA IN MADAGASCAR

[1,*]Andrianarison, M., [2]Ranaivo, I.M., [1]Raharolahy, O., [1]Sendrasoa, F.A., [4]Ramarozatovo, L.S. and [1]Rapelanoro Rabenja, F.

[1]Dermatology Department, University Hospital Centre Joseph Raseta Befelatanana, Antananarivo, Madagascar
[2]Dermatology Department, University Hospital Morafeno, Toamasina, Madagascar
[3]Internal Medicine and Dermatology Department, University Hospital Center Joseph Raseta Befelatanana, Antananarivo, Madagascar

ARTICLE INFO

Article History:
Received 04th July, 2019
Received in revised form
19th August, 2019
Accepted 15th September, 2019
Published online 30th October, 2019

Key Words:
Infantile Hemangioma, Propranol, Madagascar.

ABSTRACT

Background: Pediatric hemagioma is a benign vascular tumor and the most common tumor for children under one year. Since 2008, after the publication of C Labrèze and al., beta-blocker has become the reference treatment of all forms of infantil hemangioma. The aim of our study is to evaluate the efficacy and therapeutic tolerance of this beta-blocker in Malagasy children. **Methods:** We carried out a prospective descriptive study from 2008 till 2016 at the dermatology unit of Joseph Raseta Befelatanana Hospital Antananarivo. Our study considered all children aged less than fifteen years with infantile hemangioma and treated by oral propranolol. **Results**: In the 55 cases of pediatric hemangioma identified, there was a female predominance. Up to 73.5% of the patients carried a tuberous hemangioma; 70.5% of which with a facial localization. The mean duration of the treatment was 9.18 months with the dose of 2mg/kg/day. After the first month of treatment, a subsidence was observed in 25% of the cases and a paleness of the lesion in 74.28 %. After six months, 82.85% of the patients presented at the same time subsidence and paleness. No child presented serious side effects, demonstrating a good therapeutic tolerance. **Conclusion**: We can already say that based on its first use, Propranolol appears to be a promising treatment option of infantile hemangioma in Madagascar.

***Citation: Andrianarison, M., Ranaivo, I.M., Raharolahy, O., Sendrasoa, F.A., Ramarozatovo, L.S. and Rapelanoro Rabenja, F.* 2019.** "The Propranolol and infantile hemangioma in Madagascar", *International Journal of Current Research*, 11, (10), 7541-7543.

INTRODUCTION

Pediatric hemangiomas are the most common benign vascular tumors affecting 5 to 10% of infants under one year and 25% of premature babies weighting less than 1500 grams (Wassef, 2015). There are three types of hemangioma (Dompmartin, 2013): tuberous hemangioma, deep hemangioma and mixed hemangioma. Considering the natural and spontaneous regression of most hemangioma pediatrics within a few months, therapeutic abstention is customary. However, the expectation of this regression cannot be considered for complicated hemangiomas. Currently, beta-blockers in general, and propranolol in particular, are the first line medical treatment for complicated hemangiomas (Anderson de Moreno, 2013) or for hemangiomas at vital or functional risk. Betablockers was discovered by the French team supervised by Labrèze in 2008. Since, several studies have been published in various countries to evaluate the efficacy of this medecine on pediatric hemangiomas. The objective of this study is to evaluate the propranolol efficacy by following children treated and to estimate the possible side effects of propranolol in Malagasy children

***Corresponding author:* Andrianarison, M.,**
Dermatology Department, University Hospital Centre Joseph Raseta Befelatanana, Antananarivo, Madagascar

MATERIALS AND METHODS

We carried out a prospective descriptive study from 2008 till 2016 at the dermatology unit of Joseph RasetaBefelatanana Hospital Antananarivo. Our study considered all children with infantile hemangioma and treated by oral propranolol, aged less than fifteen years. The treatment was started from the age of three months.Location segmental hemangiomas, involving the functional or vital prognosis of the child, were the main indications of the introduction of the treatment. All cases of complicated hemangioma were treated too. A pre therapeutic checkup including a measure of fasting glycaemia, a numeration of blood formula, an electrocardiogram and a heart scan was conducted in order to look for a cardiac malformation. The presence of this disease is a contraindication for the treatment. Treatment was started from the age of three months. The administered dose started at 1 mg/ kg / day in hospital monitoring. If good tolerance is observed within fifteen days, the dose was increased by 2 mg/kg /day in ambulatory. The follow up care was done monthly. The assessment of the efficacy of the treatment was done by iconographic comparison, taken each month with dermatologists and parents appreciations. A good result is defined by paleness and regression or subsidence of the

lesions. The main known undesirable effects were systematically sought during follow-ups. The supervision of post therapeutic recurrences was done every month for the first three months, then every tree months for another year.

RESULTS

A total of 55 cases of hemangioma pediatrics requiring treatment were identified. The study included 34 females (71%) and 14 males (29%) with sex ratio of 0.41. The age of our patients averaged 7.82 months. The age group of 3 to 6 months counted 27 (55%). Faces location represented 45 children (94%). Thirty five patients presented a tuberous form (69%), followed by the mixed form in 11 cases, and deep forms in 3 cases. The mean duration of propanol treatment was 9.18 months, ranging from 5 to 13 months. Up to 42 patients (87.5%) had access cardiac ultrasound, electrocardiogram and biological assessments required by the pre-therapeutic examination. The first signs of evolution appeared on average after 1.6 months. After 1 month of treatment, 42% of the patients presented a paleness of their lesion, 25% of the patients presented at the same time paleness and regression, while 19% presented only a growth block. Fourteen percent of patients have no improvement. After six months of treatment, more than half of the patients showed a marked improvement, marked by a paleness and regression in 58% of cases (Figure 1). Only 6% of the patients had observed no change, ie no change in color and no decrease in size and thickness. The correct response of the treatment was positively correlated with the duration of the treatment (p= 0.038), regardless of the size and the age onset of the treatment. Indeed, 8.33% of patients had mild side effects that did not require discontinuation of treatment, but none had serious side effects. On one year decline in maximum after cessation of that treatment no recurrence was observed. Nevertheless, certain lesions persisted in the form of telangiectasia or a deep indurate mass in 5% of cases. These lesions concern mainly the deep hemangioma and those localized at the facial level especially in the eyelid.

DISCUSSION

The infantile hemangioma is the first benign tumor in infants that usually develops during the first few weeks following birth. Since 2008, based on Labrèze *et al* publication, beta blockers have become the treatment of reference of infantile hemangioma. Labrèze *et al* have identified some beta adrenergic receptors on the surface of endothelial cells. Propranolol had been used in children under 7 years of age for more than 40 years, especially in heart conditions. It had so far not presented any major lethal effect on children (Droitcourt *et al*., 2018). Through this study we were able to follow our patients treated by beta-blockingand evaluate the evolution of the hemangioma. In our study, the therapeutic preparation was very restrictive. All pediatric patients had to pass comprehensive cardiac and biological examinations before treatment, and they must stay for 3 days in the hospital pediatric unit. A multidisciplinary team of experts from Europe (Hoegerin 2015) recommended the preparation of treatment should only be performed in an equipped and qualified clinical environment (Hoeger *et al*., 2015). Before the start of treatment with propranolol, contraindications to treatment should be determined. An ECG is required in case of history and / or abnormal clinical examination (bradycardia, arrhythmia). Routine echocardiography is not essential unless specifically indicated by a clinical indication. The determination of blood glucose level is only necessary in premature and small babies, and in infants with a history of hypoglycaemia. All infants <2 months of age (age adjusted for prematurity), babies weighing less than 3.5 kg, and premature infants (at increased risk of bradycardia and hypotension) (Kado, 2017) require mandatory hospitalization. For older infants, hospitalization is mandatory if there is an immediate risk of endangering their lives (subglottic hemangioma) or there is significant comorbidity affecting the cardiovascular system, or when the child has insufficient social support. Blood pressure monitoring is required before, one and two hours after each dose is increased. This recommendation would help ease the financial burden on patients. The dose of propranolol varies from one country to another. In a prospective multicenter Dutch study of 174 patients in 2013, Propranolol was administered orally at an initial dose of 0.7-1 mg/kg/day divided into three doses. The dose was then gradually increased to a maximum dose of 2 to 2.5 mg/kg/day in three doses (Hermans, 2013).

According to the Labrèze team, more than 80% of cases of hemangioma start subsiding and changing color in the hours following the taking of propranolol at a dose of 2 mg/kg/day, at times superseded by a dose of 3 or even 4 mg/kg/day. Then, the effect progresses at a much slower pace, resulting in almost complete regression (Léauté-Labrèze, 2013). A European expert recommended in 2015 that the safest and most effective standard dose of propranolol is 2-3mg/kg in two divided doses with at least 9 hours of interval (Hoeger, 2015). An African team would start from 1 mg/kg/day, and then if good tolerance is observed, increases the dose to 2mg/kg/day. In our study, with a treatment dose of 2 mg/kg/day, the results are slower than those described in the literature. The first signs of evolution appeared on average 1.6 months after the start of treatment. In Madagascar, Propranolol comes in the form of a breakable tablet of 40 mg.

It is then difficult to divide this tablet into small doses. Imposing a second dose would be very restrictive and would lead to poor compliance. The duration of treatment must follow the evaluative cycle of hemangioma in order to avoid a reappearance of the lesions. According to the literature, the response to beta blockers was positively correlated with the duration of the treatment (p=0.03). This duration should last at least 12 months and shouldn't be discontinued before the age of one year when the hemangioma begins to reach its stability stage. The duration of treatment was defined according to the type of hemangioma and the therapeutic indication. The time required to treat infantile hemangioma would be 6 months with an oral solution of propranolol at a dose of 3 mg/kg/day in two doses for 1 to 5 months (Leaute-Labreze, 2015). None of our patients treated with Propranolol presented serious adverse reactions. However, according to the Dutch study, side effects exist although rare (Burne, 2014). The study, conducted in 2010, described the presence of side effects in 28 children treated with Propranolol at a dose of 1.8 - 4mg/kg/day. The side effects were triggered by either a high dose of Propranolol (4mg/kg/day) or a simultaneous administration of Propranolol and corticosteroid, causing a state of hypoglycaemia (Horev *et al*., 2015). Also, the administration of Propranolol was carried out during an episode of pulmonary infection of viral origin or during a state of fasting (repeated vomiting). Side effects (restlessness, insomnia, constipation) were observed in 14.9 %

of cases, which were more frequent in presence of prematurity (p=0.01) and hypotrophy (p=0.001). Our study corroborates with other publications regarding the effectiveness of beta blockers in the treatment of infantile hemangioma. The dose administered is certainly lower compared to those described in French or Maghreban studies, yet the period of effectiveness is comparable. Besides, unlike other studies, no side effects were observed.

Conclusion

The results obtained through this study provide a lot of hope for Malagasy children suffering from infantile hemangioma. Of course, the study requires more proof of regression of the tumor on additional cases to confirm the complete effectiveness of beta blockers. However, we can already say that based on its first use, Propranolol appears to be a promising treatment option of infantile hemangioma in Madagascar.

Conflict of Interest statement: No conflict of interest

Funding statement: There are no financial conflicts of interest to disclose

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