Efficacy and Safety of Systemic Beta Blockers for the Treatment of Infantile Hemangioma

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ABSTRACT

Background: *Infantile hemangiomas (IHs) are the commonest soft tissue tumors of infancy, with an incidence of 4% to 10% of children. Despite showing spontaneous regression following the initial proliferative phase, about 30% of cases may ulcerate, show massive growth, cause disfigurement or impact normal developmentor appearance. Common locations for problematic hemangiomas include the face, ear, orbit and airways. These hemangiomas may subsequently require early and aggressive treatment,to achieve ideal functional and cosmetic outcomes. In this study, we present the efficacy of oral propranolol in infants younger than 24 months of age, with infantile hemangiomas. This prospective cohort included 32 patients with infantile hemangiomas, attending the vascular anomalies' outpatient clinic at Cairo University Specialized Pediatric Hospital, between June 2016 and June 2018, who were treated with oral propranolol. Patients were evaluated after 7 days of treatment and then every month for a minimum of 6 months. Monthly evaluation consisted of clinical and photographic evaluations of the lesions and monitoring of treatment compliance and tolerance.* ***Results:*** *The mean age of patients was 5.48 months at the point of starting the treatment (range: 3-12 months) and was 11.64 months (range: 9-18 months) at the time of stopping the treatment. Eight males and 24 females (M:F = 1:3) were included in the study. The mean reduction of the lesion size was 36.85% (SD 11.9).Complications recorded in this study were as follows, 2 cases developed hypoglycemia (6.25%), 2 cases developed relapse after stopping the medication (6.25%) and 1 case developed hyperactivity/reactivity of the airways (3.2%). Twenty-seven cases (84%) suffered no complications, and the treatment was well tolerated in these.* ***Conclusion:*** *Propranolol is the 1st line of treatment in IHs. It is safe and well tolerated with minimal side effects.*
Keywords: *Infantile Hemangioma; Oral Propranolol; Beta Blockers.*

BACKGROUND

Infantile hemangiomas (IHs) are the most common soft tissue tumors of infancy, occurring in 4% to 10% of children under 1 year of age. Female infants are three to four times more likely to suffer from IHsthan male infants.[(1)]

Within the first weeks of life, they enter a phase of rapid growth, lasting for 3 to 6 months, which may go on for 24 months. A period of stabilization for a few months follows, with spontaneous involution usually occurring in several years. [(2)]

However, problematic hemangiomas do occur. Thosemay ulcerate, show massive growth, cause disfigurement and/or impact normal development, function or cosmesis. Common locations for problematic hemangiomas include the face, ear, orbit and airways. These hemangiomas may require early and aggressive treatment to preserve organ functional and achieve good cosmetic outcomes. Moreover, ulcerated IHs usually require treatment. For decades, systemic steroids were at the front line in IHs treatment. It was until 2008, when Léauté-Labrèze coincidentally discovered the therapeutic effect of propranolol.[(3)]

Other treatments including interferon alpha, vincristine, LASER therapy, topical imiquimod and surgical excision, have been reported to be effective alternatives. However, all of these have potential side effects and questionable or unknown long-term safety.[(4)]

In this study, we present the efficacy of oral propranolol in infants under the age of 24 months with infantile hemangiomas, focusing on size; colour; degree of flattening of the lesions; and potential side effects.

METHODS

A prospective cohort, was conducted on 32 consecutive patients with (IHs), attending the vascular anomalies clinic at Cairo University Specialized Pediatric Hospital (CUSPH), meeting the following criteria, an age of 1 to 24 months; of either gender; with IHs in the face, limbs, genitalia, trunk or natural orifices; and presenting between June 2016 and June 2018. We excluded patientsyounger than 1 month or older than 24 months; patients who received any previous treatment for the infantile hemangioma; and patient with any medical contraindications for the studied medication**.**

The study was approved by the research ethics committee of Paediatric Surgery Department, Faculty of medicine, Cairo University. We obtained an informed written consent from the parents of all patients prior to the procedures and enrollment in the study.

All patients received propranolol at a starting dose of 2 mg/kg/day, in three divided doses. The maximum dose was 3 mg/kg/day, which was an escalation policy, assigned only to cases showing no further improvement for more than 1 month on the standard dose, at any point of the treatment course. We monitored the blood pressure, heart rate and blood glucose level, 1 hour after the first dose and 4-hourly thereafter, during the first 24 hours of treatment, as an inpatient admission. In the absence of side effects, we discharged the child and treatment was continued at home.

At inclusion, full clinical assessment of the patients was carried out. We clinically examined each lesion for size, colour, and consistency. A Cardiology consultation was made for all patients prior to starting of treatment, where an examination and ECG were made. We photographed the lesions with and without a flashlight, with a standard 14-megapixel digital camera, at 30-cm distance, and approximately 2-MP resolution. An ultrasound scan was done prior to treatment and after termination of the drug therapy, to assess for reduction in size.

After discharge, we re-evaluated all the children after 7 days of starting treatment, and then monthly, for a minimum of 6 months. We continued treatment until the age of 1 year, unless complete resolution occurred beforehand. We followed the patients up for another 6 months, to detect any relapse. In case of occurrence of ant major side effects, e.g. hypoglycemia, cardiac arrhythmia or hypersensitivity to the tested drug,we managed this accordingly as an inpatient admission and withdrew the patient(s) from the study. We still followed an intention to treat analysis of outcome.

Clinical response was evaluated based on the Visual Analogue Scale (VAS), ranging from 0 to 10, by comparing follow-up images to the baseline image, taken at the time of first visit. [6] Measurements were available at time points 0, 1-week, 1-month, 3-months and 6-months. Two independent blinded examiners evaluated the images and recorded their evaluation, in comparison to the pre-treatment images.

RESULTS

The mean age of patients was 5.48 months, at time of starting the treatment and enrollment into the study (range: 3-12) and was 11.64 months (range: 9-18 months) at the time of stopping the treatment. Eight males (25%) and 24 females (75%) were included in the study.

Regarding the site of the lesions, 22 out of 32 cases (68.7%) occurred in the head and neck, 5/32 cases occurred in the trunk, 4/32 cases occurred in one of the limbs and only one case in the genitalia. With regards to size reduction, the mean reduction was 36.85% (SD 11.9). Colour fading is summarized in **(Table 1).** The mean degree of flattening is summarized as a chart in ***(Figure 1)***.

Table (1): Mean change (± SD) in the degree of fading based on the VAS

1 month	3 months	6 months
-2 (±0.9)	-3.5 (±1.1)	-5 (±1.1)

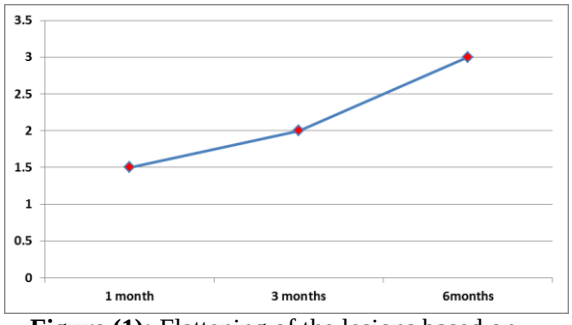

Figure (1): Flattening of the lesions based on VAS

Complications recorded in this study were as follow, 2 cases developed hypoglycemia (6. 25%), 2 cases developed relapse after stopping the medication (6.25%), 1 case developed hyperactivity or reactivity of the airways (3.125%). In 27 cases (84%), there were no complications and the drug was well tolerated.

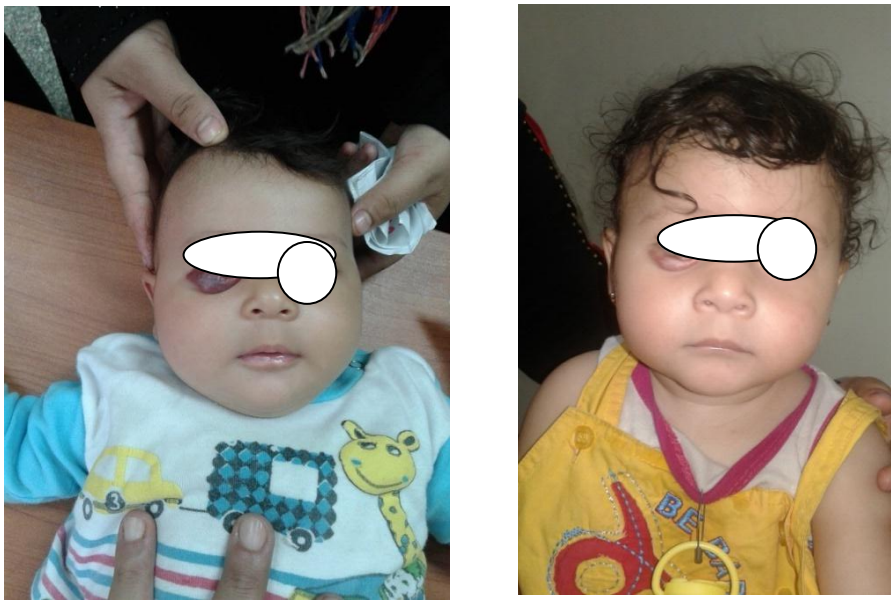

Figure (2): 5-months' old female who received propranolol for 6 months

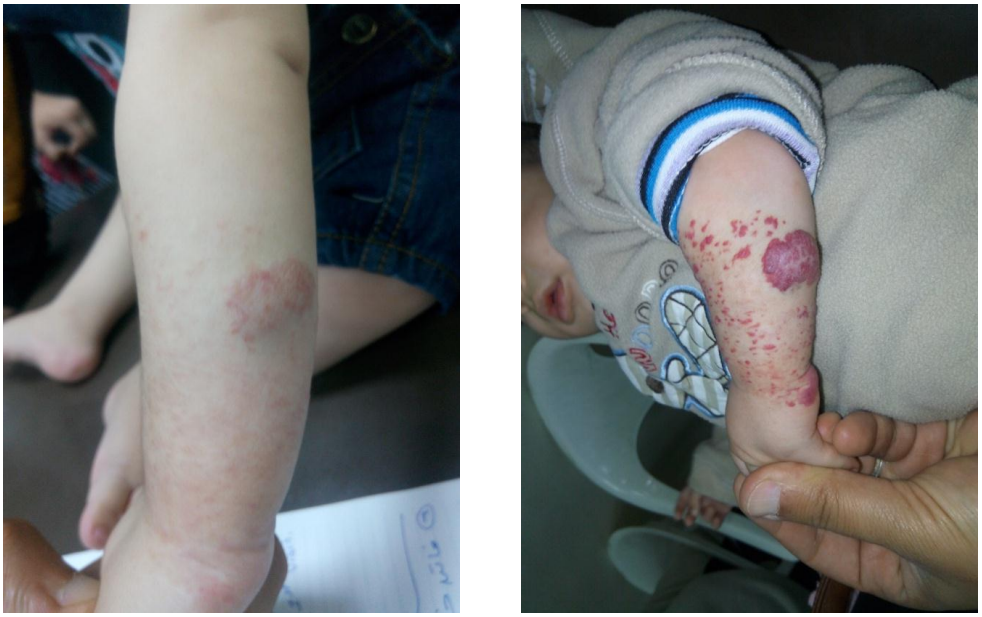

Figure (3): 8-months' old male who received propranolol for 6 months

DISCUSSION

IHs are benign proliferations of endothelial cells that can affect any part of the body (skin, mucous membranes and/or internal visceral organs), with an overall incidence of 4-10%. Over 60% of IHs occur in the head and neck region, showing female predominance of three-to-four times higher than male infants.[(1)]

IHs usually express a characteristic growth pattern. In the first weeks of life, they enter a rapid proliferative phase, lasting for 3 to 6 months, which may go on for 24 months. This is followed by a period of stabilization for a few months (plateau). Spontaneous involution usually occurs in several years.[(2)]

According to the depth of the lesion and extent of tissue involvement, IHs could be divided into three main types, superficial, deep and mixed hemangiomas. Superficial hemangiomas often present as bright red lesions, localized in the papillary dermal layer, whereas deep hemangiomas present as blue or colorless masses, localized in the reticular dermal layer or the subcutaneous tissue. Mixed hemangiomas exhibit both superficial and deep components.[(5)]

The possible mechanisms of action of propranolol on IHs are complex. These include vasoconstriction, inhibition of angiogenesis, and induction of apoptosis.[(6)]

In our study; we enrolled 32 patients presenting with IHs, who met the inclusion criteria. It included 8 males and 24 females with a male:female ratio of 1:3. Most of the hemangiomas were recognized by parents, in the 2nd to 4thweeks of life, as either a pinpoint reddish spot or painless swelling, which started to proliferate rapidly.

In our Study, 68.7% of the cases had lesions in the head and neck region, 15.6% in the trunk, 12.5% in the extremities and 3.125% were affecting the genitalia. These figures comply with the available literature.

Although most IHs do not require an urgent treatment, a minority may develop function-threatening or life-threatening complications, necessitating therapeutic intervention. About 10% of IHs cause impairment and 1% of them may cause life-threatening complications, because of their location. It is therefore prudent for pediatric surgical and medical clinicians to remain vigilant of the risk factors that may herald future complications. [(7)]

Location of the IH has a great bearing on symptoms and prognosis. An orbital apical lesion tends to cause visual defects by compressing the optic nerve. Lesions in the external auditory canal can lead to conductive deafness. Subglottic lesions present with stridor and respiratory difficulty. Early identification of the lesion is essential for prompt management, in all these situations. Therefore, location of IHsusually dictates the need for further investigations. [(8)]

Consequently, the decision whether to start treating an IH or not has usually been controversial, over the last decades, owing to the unique pattern of growth. Recent studies clarified that most untreated lesions did not improve after the age of 3-5 years, and more than 50% of untreated cases exhibited a significant residuum. Therefore, many clinicians now recommend early active intervention, rather than a conservative "wait and see" strategy. [(9)]

In 2008, Léauté-Labrèze et al., observed and reported that oral propranolol, a nonselective □-adrenergic blocker, used for decades to treat cardiac disorders in children, is effective and well tolerated in the management of IHs. A year later, they reported their experience with 32 infants with severe IHs who were treated with propranolol at 2-3 mg/kg per day, in 2-3 divided doses. These infants responded well, with a rapid, consistent and therapeutic effect. They had minimal adverse effects.At that point, beta-blockers (mainly propranolol) joined the therapeutic arsenal for IHs, even in the absence of official licensing.[(10)]

For most clinicians, treating complicated IHs, propranolol is considered the first-line medical therapy, however, optimal dosing, timing of treatment and duration are controversial. The risk of complications has not yet been fully established in randomized trials, and recommendations for monitoring are still evolving.[(11)]

In this study, we present our experience with oral propranolol, which is the 1st line of treatment of his in our practice.Ultrasonography is a reasonable initial imaging modality for diagnosing IHs because it is inexpensive and does not require sedation. The sonogram generally reveals a well-defined high-flow parenchymal

mass with possible shunting. During the involution phase, areas of increased echogenicity (fat replacement) can be seen within the lesions. Gray scale and color Doppler ultrasonography have also demonstrated practicability in monitoring the response of IHs to medical therapy.[12]In Our study, we relied on ultrasonography to measure the overall reduction of size in the lesions, after completion of the treatment, the mean reduction was 36.85% (SD 11.9).

The main goal of treatment is to reduce the cosmetic impairment of the lesions. In our study, we used the VAS proposed by Patel PKMJ et al.[13] as our reference in evaluating the results of treatment.

In respect of colour fading, this was -5 (±1.1), by the end of the treatment course. The degree of flattening of the lesions, using the VAS in the same time interval, showed improvement, especially in the first 3 months of therapy.

When hypoglycemia was noted, as occurred in 2 cases herein, we re-admitted the patient, initially increase the frequency of feds, ensure that propranolol is only given after a feed and re-tested the blood sugar, when found within normal ranges, as in our 2 cases, propranolol was continued. In the single case of reactivity/hyperactivity of the airways, we reduced the dose to be 1mg/kg/day, and the patient tolerated this. In the two cases that developed relapse after stopping the medication, we continued propranolol for another 6 months, in each case.

CONCLUSION

Propranolol, a non-cardio selective Beta-Blocker, with different mechanisms of action, is justified to be the 1st line of treatment in infantile hemangiomas in our practice. It is safe within our settings and well tolerated with minimal and manageable side effects.

Abbreviarions:

IHs: Infantile hemangiomas; **VAS:** Visual analogue scale

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