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ORIGINAL ARTICLE

PROPRANOLOL THERAPY FOR INFANTILE FACIAL HEMANGIOMA

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Abstract

Purpose: To evaluate the efficacy of propranolol therapy in infantile facial hemangioma.

Methods: Infants with facial hemangiomas who had not received either local or systemic corticosteroids were recruited. The changes in tumor size, color, and texture, and any side effects of the drug were recorded.

- A full informed consent was obtained from parents.
- Propranolol is given as an oral liquid; the initial dose was 0.5mg per kilogram of body weight per day. If the vital signs and glucose levels are normal, the dose was gradually increased over 2 weeks to 2 mg/kg/day every 8 hours.

Results: Twenty two infants (14 females and 8 males) fit the inclusion criteria and were included in this study; their mean age at presentation was 2.8 months (range 1-6). The mean duration of treatment was 2.52 ± 1.14 months and the mean follow-up period after propranolol had been stopped was 6.27 ± 2.18 months. The tumor responded to the drug and decreased in size in all of the cases (100%). No serious adverse effects were observed.

A single case showed signs of regrowth after 3 months of cessation of therapy.

Conclusion: Propranolol in a dose of 2ml /kg /day is a safe, easy and more predictable therapy for infantile facial haemangioma.Propranolol must be considered as first-line therapy in haemangioma

Keywords: β-blockers, corticosteroids, facial hemangioma, propranolol.

INTRODUCTION

Infantile hemangioma is a benign vascular tumor that involutes spontaneously by the age of10 years. . Sixty percent of hemangiomas are located in the head & neck, whereas 40% occur on the trunk and extremities.(1)

There is increased risk in premature neonates under the weight of 1500 g in females and in caucasians, and in most patients no specific treatment is required. However, in 10% of cases infantile [hemangioma is problematic or even endangering to the child, owing to its location or owing to excessive growth. In these circumstances that carry the risk of irreversible disfigurement, airway obstruction, or decreased vision,

treatment is indicated.[2]

The first-line medical treatment is corticosteroid.[3]

Steroid therapy may show no response in some hemangiomas, the side effects of steroid systemic therapy in association with the treatment of problematic hemangioma are well documented.[4]

The other medical drugs as vincristine, interferon or cyclophosphamide are used infrequent because of side effects and toxicity.[5]

The use of propranolol in infantile hemangioma therapy was discovered accidently by Leaute-Labreze et al 2008[6] during treatment 2 children for cardiopulmonary conditions.

A limited number of case series have confirmed the dramatic effect of propranolol on proliferating infantile hemangioma[7] the experience with propranolol use for infantile hemangioma is limited and concerns about their potential.

Cardiovascular and metabolic side effects have been expressed.[8]

Despite the remarkable effects of propranolol on regression of hemangiomas, little is known of its mechanism of action. A number of possible explanations for propranolol's effect have been suggested, but no evidence has been put to support these conclusions in hemangiomas. Among the suggestions for propranolol's effect of action are vasoconstriction mediated by propranolol as a nonselective β-blocker.[9]

The aim of this work is to evaluate the efficacy of propranolol therapy in infantile facial hemangioma.

PATIENTS AND METHODS

This was a prospective clinical study conducted on 22 children. At Mansoura University Hospital which is a tertiary referral center, from April 2009 to April 2012. Patients included in this study are those with facial hemangioma with no previous treatment for haemangiomas.

Thoroughly history taken, physical examination and investigations including blood picture, blood glucose, and electrolytes were done. Cardiac examination by pediatric physician and echocardiography. Patients with cardiac, airway diseases or diabetics were excluded from this study. A full informed consent was obtained from parents.

Propranolol is given as an oral liquid; the initial dose was 0.5mg per kilogram of body weight per day. If the vital signs and glucose levels are normal, the dose was gradually increased over 2 weeks to 2 mg/kg/day every 8 hours. The commercially available preparation Inderal (AstraZeneca plc, London, UK) as a 10 mg tablet was used, crushed and dissolved in 10 cc of distilled water (1 mg/cc).

Home nursing visits for 5 days to give the medication every 8 hours, to monitor vital signs and blood glucose levels.

We follow our patients up in the outpatient's clinic till the age of 1 year. During these visits, the pediatrician would ask direct questions about the possible adverse effects of propranolol, such as gastrointestinal or respiratory symptoms; monitor the heart rate, blood pressure, blood glucose, and serum electrolytes.

Changes in the tumor color, texture, or size, and any side effects of the drug were recorded and documented by photograph.

The treatment was discontinued if the lesion had completely involute clinically or if no further decrease in size was achieved despite continuation of therapy for at least 3 months. After regression of the hemangioma, propranolol is gradually stopped of by halving the concentration per dose every 3 days.

Statistical Analysis: Descriptive statistics were computed to describe the cohort. Means and standard deviations were used for continuous data and frequencies for categorical data. Analysis of variance was used to explore the predictors of good response. $p<0.05$ was considered significant. Statistical analysis was performed using SPSS version 16.

RESULTS

Twenty two infants (14 females and 8 males) fit the inclusion criteria and included in this study; their mean age at presentation was 2.8 (range 1-6) months.

They were distributed at the following sites; parotid, nose, peri-orbital, forehead, check, lips, pre-auricular and retro-auricular. They were 15 superficial, 1 deep and 6 mixed superficial & deep. (Table-1)

Table 1. Tthe site and depth of infantile facial hemangioma.

Site	Parotid	3
	Nose	3
	Periorpital	4
	Forehead	3
	Cheek	4
	Upper lip	1
	Lower lip	1
	preauricular	2
	Retroauricular	1
Depth	Superficial	15
	Deep	1
	Superficial& deep	6

The tumor responded to the drug and decreased in size in all of the cases (100%).Also there was a change in color from intense red to purple, associated with a palpable softening of the lesion, and was observed as early as 1 week after propranolol administration.

The duration of treatment range from 2.1 months to 4.3 months (mean 2.52±1.14) and the mean follow-up period after propranolol had been stopped was 6.27±2.18 months.

No serious adverse effects were observed. An acceptable decrease in heart rate and blood pressure occurred in all patients within the first month. These were considered drug effects rather than complications and did not require the cessation of therapy.

Mild hyperglycemia (above 140 mg), confirmed on three occasions, was detected in one patient after 2 months of treatment and resolved by reducing the dose to 1 mg/kg/day.

A single case showed signs of regrowth after 3 months of cessation of therapy.

Fig 1. A) Four month old child with deep and superficial hemangioma of the check and lip. B) Appearance at the age of 8 months after stoppage of propranolol.

DISCUSSION

Although benign, and known to regress with age, hemangioma variable growth pattern can lead to significant functional and cosmetic deficits in 10% of patient.[10]

In the current study the facial hemangioma occurring more frequently in females than in males, and as a solitary lesion this comes to agree with Leaute-Labreze et al. and Eivazi et al. respectively.[6,11]

Propranolol is a non-selective beta-adrenergic antagonist that revolutionized the medical management of tetralogy of Fallot and hypertrophic obstructive cardiomyopathy in the pediatric population.[12]

Propranolol is completely absorbed from the gastrointestinal tract and distributed throughout the body with highest levels occurring in the lungs, kidneys, brain and heart.so we give the drug as an oral liquid, and exclude diabetics or cardiopulmonary patients from this study.

The striking effect of propranolol on growing infantile hemangioma can be attributed to three molecular

mechanisms: vasoconstriction,[6] inhibition of angiogenesis (reduced expression of vascular endothelial growth factor [VEGF], basic fibroblast growth factor [BFGF], hypoxia inducible factor-1 alpha [fHIF-1amatrix metalloproteinase [MMP]) , induction of apoptosis or a combination of all these mechanisms.[13]

All other current drug-based therapeutic options for infantile hemangioma, similar to steroids, have been known to cause serious complications in the pediatric population. Therapy with immunomodulators such as cyclophosphamide or vincristine has been associated with myelosuppression and hepatotoxic effect. Also, serious neurotoxic effects in the form of spastic diplegia in up to 20% of cases were reported when interferon-α2a was used in treatment of infantile hemangioma.[14]

Pediatricians recite a long list of possible side effects of β-blockers including fatigue, gastrointestinal upset, nightmares, anxiety, dizziness, and bronchospasm, as well as hyperlipidemia and hyperglycemia.[15] Thus, they are relatively contraindicated in children with asthma or diabetes. B-blockers may also predispose young children especially infants, to hypoglycemia with even masking of the β-sympathetic-related symptoms,[16] but this has been reported mainly in circumstances of diminished feeding.

No significant side effects could be reported in this study as our patients don't receive higher doses (> 2 mg/kg /day) and we ensure that infant were well fed during drug therapy.

In our study there is only one partial recurrence in the deep part 3 months after stoppage of treatment in the follow up period.

Previous study have mentioned the regrowth of the hemangioma after stopping propranolol 8 weeks of stopping the drug reported in two patients when propranolol was given for a short duration and was tailed down rapidly.[17]

Bagazgoitia et al[18] reported several cases of recurrences have been reported he describe five cases of infantile hemangioma recurrence after propranolol treatment was stopped in 26 patients treated with propranolol all of whom were observed for at least 9 months after treatment was discontinued. Recurrence was present in 5 of 26 cases, yielding a recurrence rate of 19%. Early treatment withdrawal or long proliferative phases of infantile hemangioma are potential causes of hemangioma recurrence, although the exact mechanism remains unclear.[19]

In conclusion propranolol in a dose of 2ml /kg /day is a safe, easy and more predictable therapy for infantile facial haemangioma.Propranolol must be considered as first-line therapy in hemangioma when intervention is required.

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