ROLE OF ORAL PROPRANOLOL IN THE TREATMENT OF INFANTILE HEMANGIOMAS

Ari Raheem Zangana [a] and Ala Ismail Shakur [b]

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ABSTRACT

Background

Infantile Hemangiomas (IH) are the most common benign tumour during childhood. Although most of the lesions do not require any treatment, problematic IH needs some sorts of intervention. Oral propranolol by a complex mechanism of action is considered as an effective way for the treatment of IH.

Objectives

The present study was conducted to clinically evaluate the outcome of propranolol as a treatment tool for proliferating infantile hemangiomas.

Patients and Methods

In this study, 17 infants, 10 males and 7 females were included in the multicenter prospective study. All infants were in the proliferative phase. Propranolol was given at a dose of 0.5 mg/kg body weight per day in two divided doses with food for one week; then the dose increased to 1-3 mg/kg body weight according to clinical response by evaluating color, firmness, surface consistency of the lesion, depth and size ranging for a period of 4-12 months duration

Results

Most hemangiomas have elicited gradual fading of color, followed by steadily softening and decreasing in thickness of hemangiomas. Through a total no. of 17 cases before propranolol therapy, 15 cases had bright red color and 2 cases had pale color lesions. After taking propranolol therapy, only two lesions have still retained their red color, while 14 cases had clear fading of the color to pale color, and one of the cases has gained complete disappearance of the color of hemangioma to a normal skin color.

Conclusion

Within the limitations of this prospective study, oral propranolol at a dose of 1-3 mg/kg in divided doses started during the proliferative phase, had effective therapeutic responses. However, this still needs more studies to prove the safety and efficacy of the drug.

Keywords: *Hemangioma, Infantile hemangioma, Proliferative phase, Propranolol.*

[a] Department of Surgery, College of Medicine, University of Sulaimani, Kurdistan Region, Iraq.
Correspondence: ari.qader@univsul.edu.iq
[b] Ashty Hospital, Soran.

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INTRODUCTION

Infantile hemangiomas(IHs), the most common tumor of childhood, are benign proliferations of vascular endothelium. Superficial hemangiomas usually appear on the skin during the first month of life as bright red papules or plaques. Deep hemangiomas may take longer to develop and often appear as skin-colored to bluish subcutaneous swellings [1].

Infantile hemangiomas is characterized by rapid proliferation during infancy (proliferative phase), followed by slow but inevitable involution over the next 1 to 5 years (involuting phase) with continued improvement up to 10 years (involuted phase), when the cellular elements are gradually replaced by fibro-fatty deposition [2, 3].

The reported incidence of IH is 5-10%. It is higher (20%-30%) in extreme low birth weight babies, most prevalent in Caucasian children and is three times more common in female infants than males. The head and neck region is the most frequently involved area (60%), followed by the trunk (25%) and the extremities (15%) and these tumors display a non-random distribution largely correlating with regions of embryological fusion[4].

The mainstay of therapy for IH is active nonintervention (i.e., watchful waiting) as most lesions are uncomplicated and will involute spontaneously without significant sequelae [5]. Approximately 10% of these tumors are problematic [6]. Problematic hemangiomas occur when they ulcerate, have massive growth, cause disfigurement, or impact normal function or cosmetic development. Common locations for problematic hemangiomas include the face, ear, orbit, and airways.

At the end of 1960 systemic corticosteroid reported to has good response rate among children who had IH, since then it became the first line treatment of IH [7]. Other Current treatment options for problematic hemangiomas include chemotherapeutic agents (vincristine, alpha-interferon), laser, surgery, or a combination of these therapies [8, 9]. Unfortunately, each treatment option has limited therapeutic benefit with its own side-effect profile and risks [10].

Recently, Leaute-Labreze and colleagues in 2008 reported the serendipitous finding that hemangiomas regress in newborns treated with propranolol, used in treating infants with cardiac and pulmonary conditions [11].

Until now, no standardized method presents for the measurement of hemangioma treatment outcome. Because the goal of treatment is decreasing functional and cosmetic disfigurement, modified hemangioma score may be enough to meet our goals (Table 1). This score system used to assess hemangiomas clinically at evaluation sessions. It consists of color, firmness, surface consistency of the lesion, and depth (if ultrasound not affordable the score would be "0") and size ranging from 0-10 [12].

The present study was conducted to clinically evaluate the outcome of propranolol as a treatment tool for proliferating infantile hemangiomas. Objective of treatment was to inhibit further growth of the lesions and/or induce regression of it. Treatment was continued until obtaining the objective goal, or no further improvement could be attained.

Table 1. Modified hemangioma score.

Component	Quality	Score
Color	Purple to bright red	2
	Pale	1
	Skin color	0
Surface consistency	Markedly raised	2
	Raised	1
	Flat	0
Firmness	Firm	2
	Softer	1
	No firm or much softer	0
Depth	Maximal (90%-100%)	2
	Less deep (50%-89%)	1
	No depth or much less deep(<50%)	0
Size	>2% body surface	2
	1-2% body surface	1
	<1% body surface.	0
Total		0-10

PATIENTS AND METHODS

Its multicenter (Sulaymaniya, Erbil and Kirkuk) prospective study.17 infants, (10 = males and 7 = females, ratio 1.4:1) were included in the present study.

A detailed history taking, and physical examination were performed for every patient. All the infants had routine laboratory examinations, which include CBC, coagulation profile test, LFT, RFT, TFT, RBS, and urine dipstick for glucose before treatment. Patients were sent to a pediatric specialist, whenever there is any positive finding regarding the history and physical examinations, or for chest radiography and echocardiography accordingly.

Parents were thoroughly given a complete explanation about how IH grows in phases, possible therapeutic intervention modalities, and side-effects.

Following taking written informed consent from the parents, propranolol treatment was started. The diagnosis of IH based on history mainly. While in doubtful cases, radiological examination might be indicated. In our series for some cases we just depended on history because of lack of facilities.

Inclusion criteria for oral propranolol treatment of IHs in the present study included those lesions of gross size, multiple lesions, and complicated lesions including lesions with cosmetic/functional risks as well as lesions that showed rapid proliferation; all infants were in the proliferative phase of IH.

Infants with cardiovascular disorders contraindicating to propranolol use, those who were with a family history of atopy, or recent/repeated attacks of wheezing, low–birth weight newborns especially in whom energy intake is low and they were at risk of hypoglycemia, and also patients who received other treatment modalities before were excluded from the present study.

Propranolol has been given at a dose of 0.5 mg/kg body weight per day in two divided doses dissolved in small amount of milk or juice with food or directly after meal. Blood pressure and heart rate were measured after one hour of starting propranolol treatment. All patients stayed at hospital for around 4 hours. In the absence of any side effects, the drug treatment was continued at home.

Infants were reevaluated after one week, propranolol dose is increased to 1mg/kg body weight per day, then the patient is seen in the next two weeks to evaluate the compliance and tolerance of the drug, and to adjust the dose accordingly. The final dose adjustment is 1-3 mg/kg/d in divided doses according to the clinical response, patient's tolerance, clinical behavior of IH.

Further, follow ups were done by either patient visits or telephone interactions whenever any unwanted event happened, or the parents were suspicious about something.

The course of treatment lasted 4-12 months depended on the degree of regression of the hemangiomas. Dose of oral propranolol was altered according to the weight changes and the patients' response at follow-up visits. Then the medication of oral propranolol was tapered by decreasing to one-half dose for two weeks, then to one-quarter dose for the next two weeks and then discontinued completely.

The drug was stopped if the lesion continues to grow despite the regular administration of treatment, if the patient experienced unacceptable adverse effects of the drug, or if there was lack of compliance of the parents.

Photo documentation was obtained before starting treatment as well as at each follow-up visit. Monitoring of treatment compliance and tolerance (heart rate and blood pressure) as well as measuring the body weight for dosage adjustment was done at each visit. Ophthalmologic examination for assessment of infants with eyelid involvement was done as needed.

The change in the hemangioma score values was evaluated by using paired t test by SPSS program, comparing the different follow up visits. All tests were 2 tailed and Correlation is significant at the 0.05 level.

RESULTS

The age of the patients was between one to twelve months, the mean age for initiation of treatment was six months, from October 2016 till March 2018. Thirteen infants (76.5%) were less than 6 months of age, while 4 infants (23.5%) were more than 6 months of age. (Fig.1).

Patients with 22 IHs at different body regions, locations include head (n = 13)76.5%, body (trunk and extremities) only (n = 1), and multiple in both head and body (n=3) (Fig.2).

Early treatment was indicated for rapidly proliferating lesions including those with cosmetic and/or functional risks. Chief complaints were cosmetic disfigurement (n=10) 58.8%, ulceration and bleeding (n=4), visual

obstruction (n =2), and feeding problem (n = 1) as shown in (Fig. 3).

Patients' demographic data are summarized in Table 2. Most hemangiomas, after treatment with propranolol at different periods, have elicited color changes from bright red to pale, followed by a gradual fading of lesions' color (Fig. 4). Through a total no. of 17 cases before propranolol therapy, 15 cases had bright red color and 2 cases had pale color lesions. After taking propranolol therapy, only two lesions have still retained their red color, while 14 cases had clear fading of the color to pale color, and one of the cases has gained complete disappearance of the color of hemangioma to a skin color.

These data could be objectively proven by the statistically significant color change (p =0.046).

In addition to color changes, there was a noticeable decrease in surface consistency from markedly raised to raised and/or flat followed by regression in sizes, after propranolol treatment (Fig. 5). These changes can be significantly proven by the statistically significant changes in the surface consistency (p = 0.026) and size of the lesion (p < 0.01).

Collectively, these clinically elicited changes in color, size, surface consistency and firmness "proved by statistically significant changes in lesions (p value = 0.040)" was obvious in IHs on propranolol therapy. Fig (6) and Table 3.

Among a total number of 17 cases, 1 patient (5.9%) was considered to have complete resolution after a period of one-year treatment starting soon after birth (Fig. 7).

One child (5.4%) from the group given propranolol at a dose of 2 mg/kg, developed irritability and somnolence. However, the adverse effect was temporary and disappeared after decreasing the dose of propranolol. On the other hand, we stopped the treatment of one child because of lack of compliance of the parents.

Over all, propranolol treatment at a dose of 1-3 mg/kg body weight per day in divided doses has proven to be well tolerated and effective modality of treatment for IHs resulting in considerable shortening of the natural occurring course of IHs.

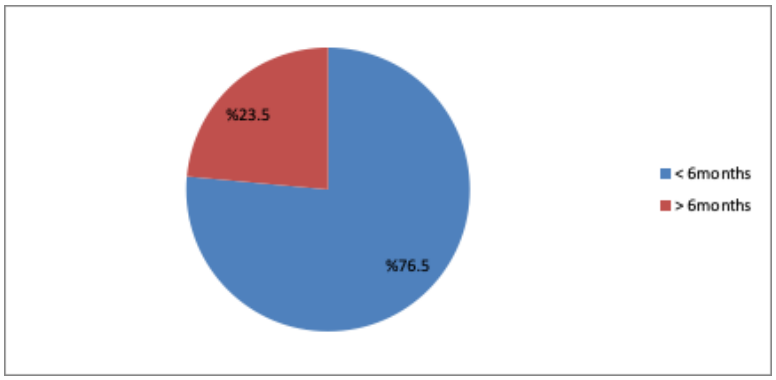

Figure 1. Age of patients.

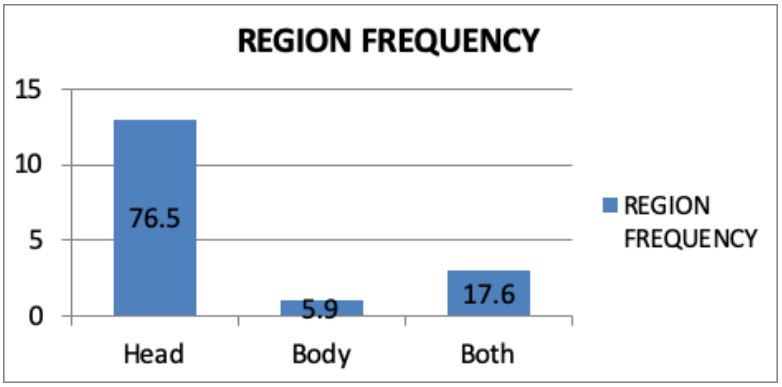

Figure 2. Regions of IH (0 head, 1 body, 2 both).

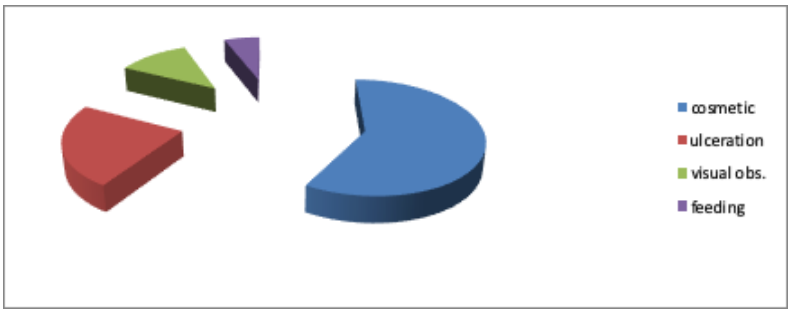

Figure 3. Chief complaints.

Table 2. Patients' demographic data before treatment.

Category	Subcategory	No. of Patients	Percentage
Sex	Male	10	58.8%
	Female	7	41.2%
Age	<6 months	13	76.5%
	>6months	4	23.5%
Birth	Preterm	4	23.5%
	Term	13	76.5%
Region	Head	13	76.5%
	Body	1	5.9%
	Both	3	17.6%
Site of IH in head	Eye	2	11.8%
	Nose	1	5.9%
	Lip	6	35.3%
	Other areas	4	23.5%
	Half face	2	11.8%
Presenting complaints	Cosmetic disfigurement	10	58.8%
	Ulceration and bleeding	4	23.5%
	Visual obstruction	2	11.8%
	Feeding and breathing problems	1	5.9%

Figure 4. Gradual color change in IH in the breast and areolar area.
A. Pretreatment, B. After one month, C. After 3 months of oral propranolol.

Figure 5. Decrease in size of IH. A Before treatment, B. After one month of oral propranolol.

Table 3. Clinical change and statistical analytic result in pre and post propranolol treatment of modified hemangioma score.

Component	Quality	No. of cases pre-treatment	No. of cases post treatment	P value
Color	Purple to bright red Pale Skin color	15 2 0	2 14 1	0.046 Significant at:0.05
Surface consistency	Markedly raised Raised Flat	10 6 1	3 10 4	0.026 Significant at:0.05
Firmness	Firm Softer No firm or much softer	12 5 0	2 12 3	0.07 Significant at:0.05
Size	>2% body surface 1-2% body surface <1% body surface.	3 2 12	2 3 12	0.00 Significant at:0.01
Total				P.value 0.040

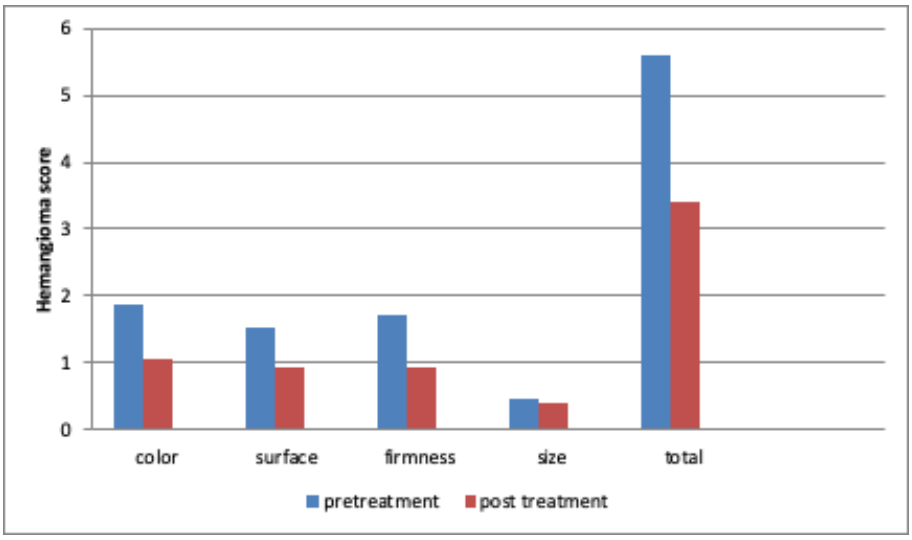

Figure 6. Results of modified hemangioma score at the final follow up.

Figure. 7. Complete resolution of IH.

DISCUSSION

In our prospective study, we chose oral propranolol in those children who has a problematic IH. The age of our patients was between 2 to 12 months (mean age six months). i.e. all of them were in proliferative phase of hemangioma. The purpose behind that, it has been shown by many previously published studies that early treatment with oral propranolol, especially when started during the proliferative stage has better long-term outcomes [13].

In this series, 13 cases (76.5%) were less than six months of age, while 4 cases (23.5%) were more than 6 months and less than 12 months, but there was no significant difference in improvement between these two groups (i.e., no significant correlation value > 0.05). Our result is not harmonious with the study done by Jing Ge et al. Oral propranolol combined with topical timolol for compound infantile hemangiomas: a retrospective study in which their result showed more improvement among those children who were less than six months of age, rather than those who were older [14].

On the other hand, Female/male ratio was 1 to 1.4, which is not in agreement with current literatures, in which the predominance of IHs in females has been observed. These disagreements mostly belong to small sample size and need to be repeated to a wider population in large study.

During oral propranolol therapy in the present study, the first noticeable change was continuous fading of color as well as softening of the lesion and decrease in thickness, these all changes contribute to regression in size. These clinical changes in color, thickness and size have been fairly proven by statistically significant changes at lesions' score totally (p value < 0.05). Our results are consistent with the study made by Hogeling et al., a randomized, controlled trial of oral propranolol in infantile hemangioma [15].

E. Baselga in de la Santa Creu i Sant Pau hospital, Barcelona, Spain in 2011 described that IH receiving propranolol at a dose of 2mg/kg/d responding so rapid as color change will be seen within the first week [16], this rapid response was not happened in our case series, we saw obvious color change nearly after one month of propranolol treatment (Fig. 4). The good reasons explaining this mismatch in response might be, First: we have started oral propranolol with a very low dose which was 0.5 mg/kg/day then after one week, we have

gradually increased the dose as we treated our patients as an outpatient cases this, will obviously leads to delay in therapeutic response. Second: non-availability of propranolol in a pharmaceutical formulary dose appropriate for newborns and infants in my country. For our cases, oral propranolol was prepared from tablets dissolved to smaller dosages, which may complicate dose adaptation and drug administration.

Through a series of 89 cases by a study made by Xiaohan Liu et al. 2015 in China, seven children (7.8%) developed side effects: which was cold extremities (3.4%), sleep disturbance (2.2%), and GIT problems (2.2%) [17], which was not coincides with another series of 30 cases by SérgioLaranjo et al. in 2013, in that one has developed any side effect [18].

While in our study, one case (5.9%) developed difficulty sleeping and irritability, which was temporary and disappeared after decreasing the dose. No, any other side effects happened to a total of 17 cases. Despite the safety of drug, we should keep in mind the reported side effect of propranolol might happen so the consultation of pediatric and cardiologist is highly indicated in suspicious cases.

This study is limited in that a direct comparison to other treatment modalities has not been done. Also, the lack of control group with spontaneous resolution is another limitation in the present study. Nonetheless, this preliminary report supports the use of propranolol in problematic hemangiomas as an effective treatment tool and can be used in proliferative infantile hemangiomas to shorten its course.

Future comparative studies including larger number of patients and longer follow-up time should be addressed to determine the efficacy, safety and long-term outcome of this treatment.

In conclusions, within the limitations of this prospective study, oral propranolol at a dose of 1-3mg/kg in divided doses started during the proliferative phase has shown efficacy and tolerance with few expected adverse effects, therefore, it can be used as an effective mean of treatment in patients with IH when intervention is required.

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