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CLINICAL EVALUATION OF THE ORAL PROPRANOLOL EFFICACY AND SAFETY IN THE TREATMENT OF INFANTILE HEMANGIOMA

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ABSTRACT

Background: Infantile hemangiomas (IH) are common, benign, self-limiting endothelial cell tumor in infants. Although IH are likely to improve or regress with time, cases with cosmetic disfigurement and functional disability required specific treatment.

Objectives: To evaluate the effectiveness and safety of oral propranolol in Iraqi infants with hemangioma.

Patients & Methods: This prospective and clinical therapeutic study was conducted in Basra Teaching Hospital in the south of Iraq during a period between the first of September-2012 to the end of the November -2013.A total of 30 infants, up to 12 months of age with infantile hemangiomas were included in this study. They were treated with oral propranolol, 2 mg/kg per day divided in 2 doses for 6 months duration. Changes in the size, surface and color of the hemangiomas were recorded at regular interval. The treatment response was evaluated clinically using 3- points scale system: good, partial, and no response. Propranolol adverse effects were evaluated and managed accordingly. All infants were followed for 4 months.

Results: This study showed that oral propranolol induced remission and good response in 93.3% of patients (28 patients)after 24 weeks treatment course ,in addition ,it has been shown that earlier treatment of hemangiomaswith oral propranolol induced good response in 100% of cases in comparison to the late treatment ,where good response was reported in 85.7% of cases . No major side effects were reported in treated children .None of the treated hemangioma was recurred after cessation of treatment.

Conclusion: Oral Propranolol at therapeutic doses, is found to be an effective and safe treatment of infantile hemangiomas particularly among those who are treated early within first 6 months of life

KEYWORDS: Infantile Hemangioma, Propranolol

INTRODUCTION

Infantile hemangiomas are common, benign, usually self-limiting endothelial cells tumors of infancy ; they are proliferative lesions , usually appears during the first weeks of life (1,2). They have unique biphasic growth behavior (2,3). The unique growth characteristic of hemangioma which can be divided into 3phases (2):

- Proliferation phase
- Involution phase
- Involuted phase

The phase of rapid growth is usually most pronounced during the first 3 to 6 months, followed by a phase of slower growth, between the middle and end of the first year of life (3,4). The involutional phase of an infantile hemangioma may be rapid or prolonged. No specific characteristics appear to influence the rate or completeness of involution of infantile hemangiomas(1,3) , 50-70% percent of infantile hemangiomas complete involution by age 5 -7 years , while the remainder may take an additional 3-5 years to complete the process.

The first step in the management of infantilehemangiomas is to identify whether it is a low-risk /uncomplicated or high-risk/complicated hemangioma (15, 17).A hemangioma that is asymptomatic, small in size, non-ulcerated and does not have the potential to impair a vital function is called low-risk or uncomplicated hemangioma. For these forms of lesion, it is generally enough to observe them.

Treatment should be considered in the following circumstances (21, 23):

- Very large and unsightly lesions
- Ulcerating haemangiomas (up to 5-25% of lesions)
- Lesions that impair vision, hearing, breathing or feeding
- If they fail to resolve by school age

The possible treatments include [23,26,27]:

- External compression therapy (bandaging the limbs)
- Ultra potent topical steroids.
- Topical antiseptics. Eosin, which also has antiangiogenic properties, has been reported to be of benefit.
- Oral corticosteroids in high dose, during the proliferative stage of segmental disease.
- Sometimes, intralesional steroid injections have been used for small haemangiomas.
- Vascular laser therapy at age 3 to 4 years, when lesions are stable
- Interferon alpha may be useful but is rarely recommended, as it has been associated with the development of cerebral palsy in a few infants.
- Vincristine was reported effective in the past but is rarely used today
- Imiquimod has been reported to speed resolution in some cases [51].
- Propranolol is rapidly becoming the treatment for troublesome haemangiomasand is the subject of several current research trials[33, 35].

PATIENTS AND METHODS

This prospective, clinical therapeutic study was conducted in Basra Teaching Hospital during a period between the first of Septemper-2012 to the end of the November-2013. Thirty infants (24 females; 6 males) presented with 42 IHs of different types, at different body regions, were included in the present study.

The patients were divided into two groups according to their ages: ***Group Aincludes*** infants whose ages are ≤ 6 months (16 infants) and ***Group B*** infants older than 6 months of age (14 infants).

Every patient was subjected to a thorough history taking and physical examination to ascertain risk factors or contraindications to using propranolol. Specific questions pertaining to reactive airway disease, asthma, lung or heart problems, hypoglycemia, and reflux are asked. Parents were thoroughly given complete information about how infantile hemangioma grows in phases, possible treatment modalities, and side effects. After written informed consent was obtained from the parents, propranolol treatment was started. Ethical approval was confirmed from Scientific Council of Dermatology and Venereology of the Iraqi board for Medical Specializations.

Baseline electrocardiograms (ECG) were conducted and interpreted by a pediatric cardiologist for all treatment candidates. Prior cardiac history, suspected heart blocks, or other abnormal findings on ECG warrant an echocardiogram prior to therapy initiation. Patients with a history of prematurity, lung, or cardiac conditions are admitted for over-night monitoring at the onset of propranolol treatment.

Inclusion criteria are any infants with cutaneous hemangiomas (single or multiple) while exclusion criteria are any child with a cardiovascular disorders, bronchial asthma, insulin dependent diabetes mellitus, recent or repeated outbreak of wheezing and visceral haemangioma or who received previous treatment prescribed for infantile hemangiomas**.**

Propranolol was given at a dose of 2 mg/kg body weight per a day in 2 equally divided fixed doses before feeding for 24 weeks period of therapy. For standardization purpose, propranolol crushed tablet was dissolved in clean water with sugar then given orally by teaspoon for all included children. First dose was given to the patients in dermatology department. Blood pressure and heart rate were monitored shortly after starting propranolol treatment. In the absence of side effects, treatment was continued at home, and infants were reevaluated on weekly basis at first month, every 2 weeks in the second month, and then every month till the end of treatment. Propranolol is weaned at the end of treatment, as recommended by our cardiology team for most beta-blockers, by reducing the dose by one half for 1 to 2 weeks, then stopping. Finally, all infants were followed up for up to 4 months after cessation of propranolol treatment. Mothers were informed about proper dose, mode of administration and sign of oral propranolol side effects like fainting, restless sleep, irritability and mood disturbance.

All patients in each visit were subjected to full evaluation including clinical exanimation of hemangiomas, propranolol side effects and assessment of response as well as measuring of body weight for dosage adjustment.

Baseline photograph was carried out before starting treatment as well as at each follow-up visit using high resolution Sony Cyber Shot digital camera 12 megapixels.

The response to the treatment was evaluated by interval clinical examination of hemangioma (at 4^{th} weeks, 12^{th} weeks and at the end of 24^{th} weeks of treatment) according to 0%-to-100% scale: [(39)]

- **Poor Response**: regression or cessation of growth (denotes 25% or less regression).
- **Fair Response**: shrinkage or flattening of the lesion (denotes 26% to 50% regression).
- **Good Response**: lighting of the surface color (denotes 51% to 75% regression).
- **Excellent Response**: complete clearance of hemangioma or leaving faint red color (denotes 76% to 100% regression).

Statistical Analysis

Results are presented in numbers, percentages, mean values ± SD, and ranges. Data were statistically analyzed using the Chi square test using the Statistical Package for Social Sciences (SPSS software v. 20) and statistical significance was set at $P \leq 0.05$.

RESULTS

- **Demographic Data**

Thirty infants were included in this study, their mean ages ± SD were **5.9±3.36** months (range 1-12 months), 6 were males and 24 were females with female to male ratio 4:1. Family history for hemangioma was positive in 6.6%. Seventeen (56.6%) infants had hemangioma since birth while 13 (43.4%) appeared later after birth. Nineteen (63.3%) infants were of skin type III, 8 (26.7%) skin type II and 3 (10%) skin type IV. (**Table -1**)

- **Infantile Hemangiomas' Data**

Eighteen (42.9%) lesions were superficial type (capillary infantile hemangioma), 17 (40.5%) mixed infantile hemangioma while only 7 (16.7%) cavernous type. Regarding location of hemangiomas; 31 (73.8%) lesions were located on head and neck, 8 (19%) on trunk, 2 (4.8%) on extremities and one (2.4%) on anogenital region. (**Table -2**)

- **Response to Propranolol Therapy**

The early clinical response of hemangioma to oral propranolol therapy that occurred within the first week of treatment was the change in the hemangioma color from bright red to faint red while the flattening and size regression occurred later.

Out of 30 patients with infantile hemangioma, 23 (76.7%) patients showed excellent response (76% to 100% regression in size), 5 (16.7%) showed good response (51% to 75% regression), and 2 (6.7%) patients showed fair response (26% to 50% regression). No one had regression or cessation of growth of hemangioma.

In this study, the early clinical response of hemangioma to oral propranolol therapy that occur within the first 4 weeks of the treatment as 3 (10%) infants had fair response, 8 (26.7%) good response, 19 (63.3%) excellent response and no one had poor response. After 12 weeks, one infant with fair response at 4 weeks had an excellent response. After 24 weeks, three patients with good response at 4 and 12 weeks developed an excellent response. **(Table -3)**

The response to oral propranolol was not affected by the age of infants (below and above 6 months) presenting with hemangioma when starting therapy (p value= 0.205). **(Table -4)**

Although there was no statistical difference between both groups in response to oral propranolol, but clinically all infants (100%) less than 6 months of age showed more than 51% hemangioma regression in comparison with 85.7% of those aged more than 6 months as a rapid response, minimal noticeable residual changes and better outcome were evident obviously in infants younger than 6 months of age. **(Table -4)**

In addition, there was no significant difference in the clinical response to propranolol in relation to gender of infants (p value= **0.206**). **(Table -5)**

Table 1: Patients' Data at Initial Presentations

Demographic Data		N	%
Age group	Less than 6 months	**16**	**53.3%**
	More than 6 months	**14**	**46.7%**
Gender	Male	**6**	**20.0%**
	Female	**24**	**80.0%**
	Female/male ratio	**4:1**	
Family history	Positive	**2**	**6.6%**
	Negative	**28**	**93.4%**
Onset	Since birth	**17**	**56.6**
	Later after birth	**13**	**43.4**
Skin type	II	**8**	**26.7%**
	III	**19**	**63.3%**
	IV	**3**	**10.0%**
Age at initial presentation (months)	**5.9±3.36; (range 1-12)**		

Table 2: Infantile Hemangiomas' Data at Initial Presentations

Infantile Hemangiomas' Data		N	%
Types of IHs	Superficial	**18**	**42.9**
	Cavernous	**7**	**16.7**
	Mixed	**17**	**40.5**
	Total	**42**	**100.0**
Location of IHs	Head and Neck	**31**	**73.8**
	Trunk	**8**	**19.0**
	Extremities	**2**	**4.8**
	Anogenital	**1**	**2.4**
	Total	**42**	**100.0**

Table 3: Response to Treatment after 4, 12 and 24 Weeks from Treatment

Response Score	After 4 weeks		After 12 weeks		After 24 weeks	
	N	%	N	%	N	%
Poor response	0	0.0%	0	0.0%	0	0.0%
Fair response	3	10.0%	2	6.7%	2	6.7%
Good response	8	26.7%	8	26.7%	5	16.7%
Excellent response	19	63.3%	20	66.7%	23	76.7%
Total	**30**	**100%**	**30**	**100%**	**30**	**100%**

Table 4: Response to Treatment in Both Groups in Relation to Age

Response Score	Less than 6 Months		More than 6 Months		Total		P Value
	N	%	N	%	N	%	
Poor response	0	0.0%	0	0.0%	0	0.0%	**0.205***
Fair response	0	0.0%	2	14.3%	2	6.7%	
Good response	2	12.5%	3	21.4%	5	16.7%	
Excellent response	14	87.5%	9	64.3%	23	76.7%	
Total	**16**	**100%**	**14**	**100%**	**30**	**100%**	

*Pearson Chi square was used

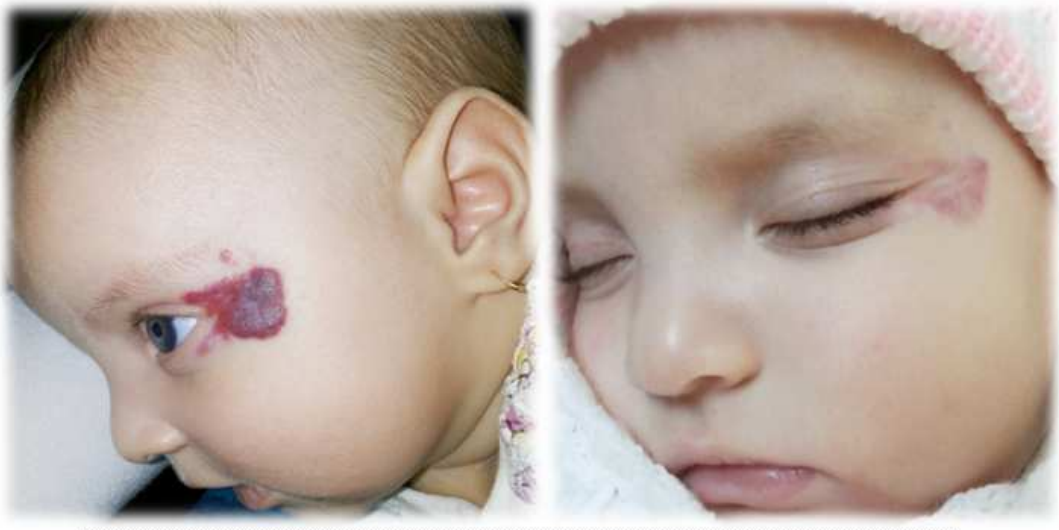
Table 5: Response to Treatment in Both Groups in Relation to Gender

Response	Male		Female		Total		P value
	N	%	N	%	N	%	
Poor response	0	0.0%	0	0.0%	0	0.0%	
Fair response	0	0.0%	2	8.3%	2	6.7%	
Good response	1	16.7%	4	16.7%	5	16.7%	**0.706***
Excellent response	5	83.3%	18	75.0%	23	76.7%	
Total	**6**	**100.0%**	**24**	**100.0%**	**30**	**100.0%**	

*Pearson Chi square was used

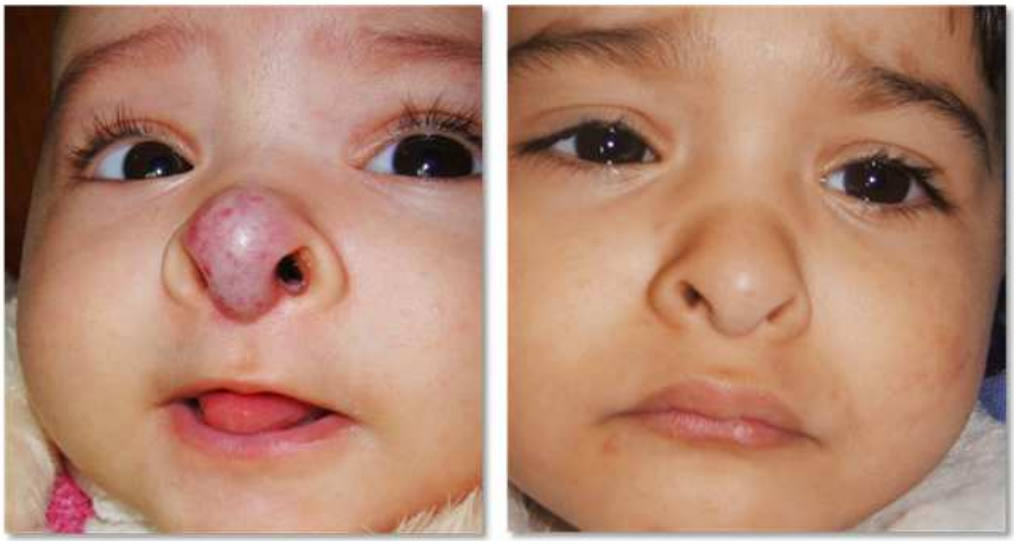
Before **After**

Figure 1: Resolved Infantile Hemangioma by the End of the 24 Weeks of oral Propranolol Therapy in the One Month Female Baby



Before **After**

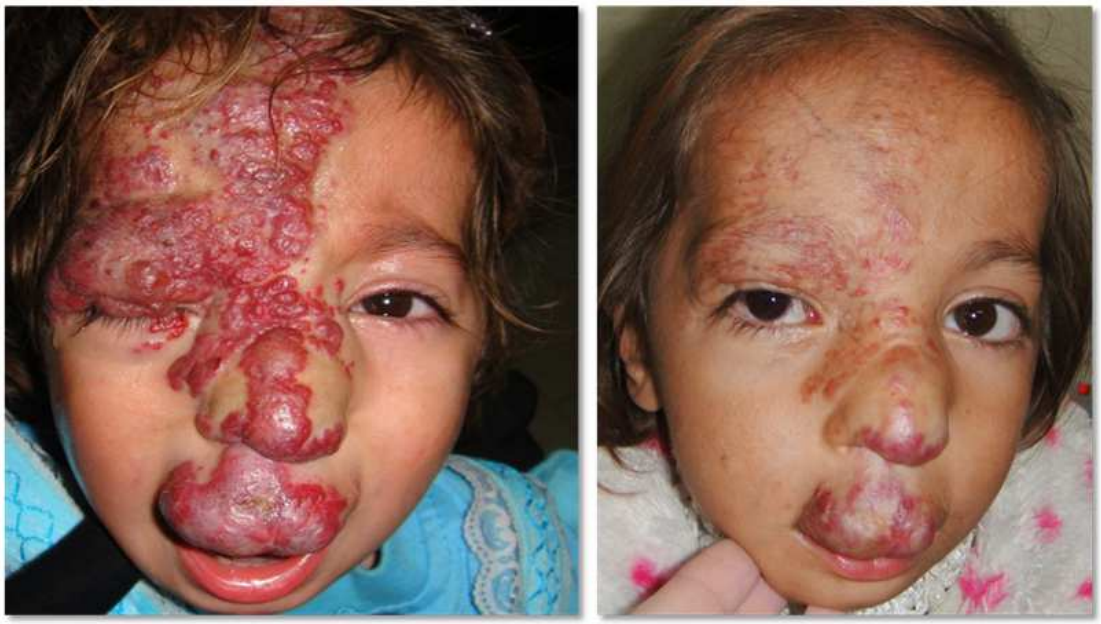
Figure 2: Two Months old girl with Strawberry Hemangioma; 24 Weeks after Commencing of Treatment with Propranolol Therapy , Hemangioma Shows Marked Regression with Residual Faint Shadow



Before **After**

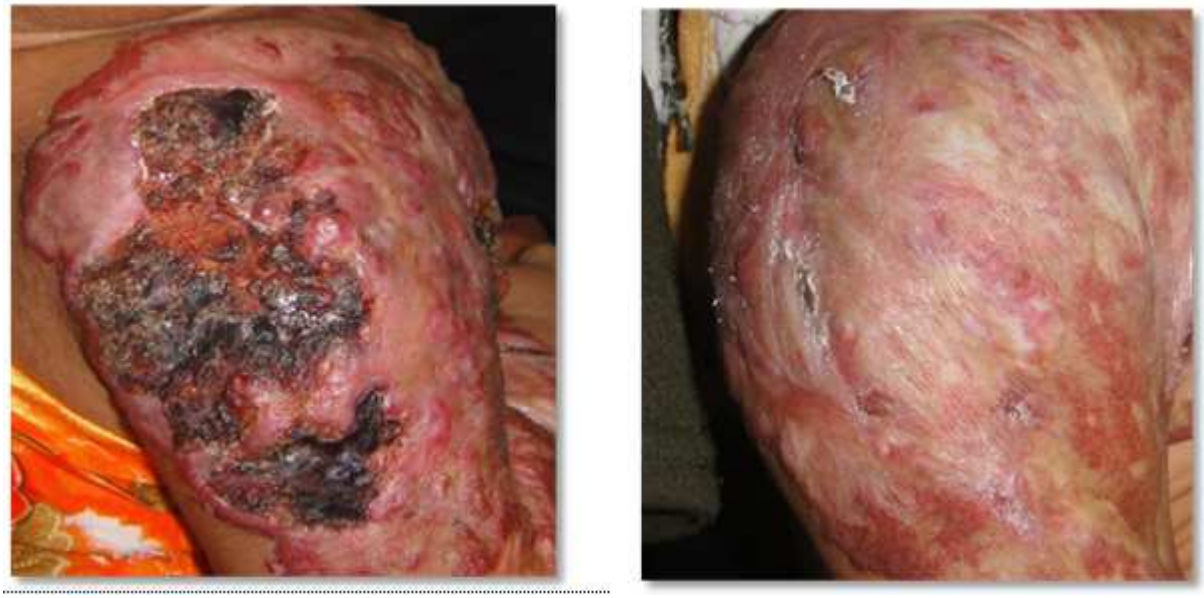
Figure 3: Frontal View for Female Patient with Hemangiomas of the Nasal tip Demonstrated a Good Clinical Improvement after Treated with oral Propranolol for 24 Weeks Period

On the other hand ,in this study ,although 2 patients (6.7%) with infantile hemangiomas showed partial response to oral propranolol therapy, but the effect of propranolol on their hemangioma was clinically evident and satisfactory to parents of treated child(figure 4, 5).



Before **After**

Figure 4: 12 Months old Female Patient with Infantile Hemangioma Involves 2 Facial Segments: Seg1 (Frontotemporal) and Seg4 (Frontonasa) ; Regression of Size, Flattening of the Surface and Blanching of the Color of the Lesion was Evident at 24 Weeks of Oral Propranolol Therapy



Before **After**

Figure 5: 10 Months Old Female Baby with Ulcerative Infantile Hemangioma Involving Upper arm; Healing of Ulcerated Area with Flatting of the Lesion was Achieved by Oral Propranolol

DISCUSSIONS

Hemangioma is a benign tumor composed of hyperplastic vascular endothelium. Infantile hemangiomas of infancy are common, benign, self-limited tumors (8), although, it is often difficult to predict the progress and prognosis of hemangioma during the first few months of life. Moreover, the unpredictable outcome after proliferation and proposed involution of infantile hemangiomas, and because there is no way to predict the size that hemangiomas can reach, a significant percent of hemangiomas are associated with substantial morbidity in infancy and childhood such as disfigurement, psychosocial distress for patient and family and threats to life or function) (2, 3) that is why therapeutic interventions are frequently indicated in many cases.

Despite many treatments that have been described for the treatment of hemangiomas, there is no currently well-studied or FDA approved systemic therapy for infantile hemangiomas except for propranolol. The US Food and Drug Administration (FDA) have approved a pediatric formulation of propranolol hydrochloride for treatment of proliferating infantile hemangioma requiring systemic therapy (40).

Recently, reports of successful treatment of infantile hemangiomas with propranolol have been published which was described for first time in 2008 by Leaute –Labreze et al (14), but little is known regarding the propranolol proper dosing, mode of administration and long-term outcomes, in addition to the small sample size of many published studies where the conclusions are not scientifically and statistically solid. (38)

This study showed that oral propranolol achieved good response in majority of the cases (93.3 %) within 12 and 24 weeks duration of treatment.

The rate of response that have been reported in the present study is higher than that of other studies , using different dose regimen (2 mg/ kg/ day in 3 equally divided doses), Hermanset al showed that 60% of their patients had

complete resolution of the lesion. (41)

In addition, this study achieved a higher response rate than that reported by Holmes et al (42) using higher dose (3 mg/ kg/day) with response rate (87%).

None of the treated patients in this study was resistant to treatment or not respond to oral propranolol therapy , in contrast to that reported by other studies (42, 43) .

As well as none of the patients in the present study showed evidence of recurrence or rebound growth of hemangiomas (increase in the size or worsening of the color) after cessation of therapy in comparison with other studies in which the rebound growth was reported. (43, 44)

The high response rate and the significant clinical results along with lack of recurrence in the present study in contrast to other studies are probably attributed to:

- The present study showed that oral propranolol, at 2mg/kg/day/in 2 equally fixed divided doses, is effective regimen in the treatment of infantile hemangioma associated with higher response rate than the dose regimen adopted by other studies **(42-45)**
- In the present study, oral propranolol was given as a crushed tablet dissolved in sugared water that was given orally by spoon before feeding for all included children. This is shown to be more tolerable by the child and it decreases the likelihood of gastro esophageal reflux in contrast to other studies **(38)**, which may lead to improper dose and decreasing the efficacy of the given drug.
- The marked good response and lack of recurrence indicate that propranolol achieved permanent resolution of hemangiomas, which occur earlier than the expected resolution through the natural course of the disease which is said to be completed by the age of 5 -7 years in 50-70 % of the cases, in addition to the risk of disfigurement and complication that may be serious and interferes with the function of vital organs.

Propranolol is thought to exert its effects on hemangioma by two mechanisms **vasoconstriction and antiangiogenic** effects. Propranolol as β-adrenoceptor antagonist inhibits vasodilatation mediated by adrenaline leading to vasoconstriction with subsequent reduction of blood flow within the lesions resulting in the reduction in the depth of the color of treated hemangioma that is reported to be the first sign of clinical response occurring within hours (4-6 hours) of starting therapy. **(34, 35)**

Propranolol as β-receptor blocker also leads to a reduced expression of pro-angiogenic factors: vascular endothelial growth factor, VEGF and basic fibroblast growth factor, bFGF, on endothelial cells which is increased during proliferation of hemangiomathus angiogenesis is inhibited with the subsequent decrease in the size of hemangioma and flatting of the lesion with further reduction in the depth of its color, this is possibly explained the marked reduction in the size of the treated hemangioma within the first week of treatment with subsequent significant regression of hemangioma. **(6, 8)**

The present study also showed that there was clinically significant difference in the clinical response between patients younger than 6 months of age and those who were older, where good and excellent response was reported in 100% of the patients younger than 6 months of age, in contrast to 93.3% among those who were 6 months of age and older, although there was no statistically significant difference between these two groups, the rapid response, minimal noticeable

residual changes and better outcome was evident obviously in patients younger than 6 months of age.

This clinical difference in rate of response highlights that the propranolol is more effective in the early proliferation phase that is commonly pronounced during the first 3 to 6 months of life. There was no significant difference in the clinical response in relation to sex of patient.

Although the fair response is reported in **14.3%** of the cases , but we thought that, oral propranolol achieved another goal of treatment as it induces gradual re-epithelialization of ulcerated hemangioma with complete resolution of symptoms that was achieved with in the first 4 weeks of treatment .In addition, ultimate reduction in ugly looking hemangioma , reducing the interference of hemangioma with the function of vital organ a long with satisfaction of parents of treated child achieved a remarkable reduction in the psychological impact of the child hemangioma on his parents which we think is an important outcome of any used medication. Moreover, the partial response to oral propranolol in this study is probably comparable, if it is not better, than that of other modalities of treatment for such type of hemangioma.

In addition, we think that oral propranolol is useful when given prior to other therapeutic modalities, to reduce the size of hemangioma, thus making it more amenable to treat with surgery, laser and other to achieve better result.

Moreover, unlike other studies that have shown successful response of ulcerated hemangiomas to oral propranolol, none of the patients in present study had received any previous therapy prior to oral propranolol treatment for ulcerated hemangioma, where at least one of the following treatment modalities including: topical and/or systemic antibiotics , pulsed dye laser therapy , or oral corticosteroids has been used prior to starting therapy with propranolol [44, 46] , so this makes the present study superior than others in this points, because the clinical improvement of ulcerated hemangioma in the present study is attributed only to the action of oral propranolol .

In this study, none of the patients showed serious side effects neither during the treatment, nor during follow up period.

Moreover, in this study, regimen of 2 mg/kg/day in 2 equally fixed divided doses before feeding for 24 weeks is showed to be safe and associated with no serious side effects, in addition to its high efficacy and tolerance.

Exclusion of patients with personal or family history of cardiac and respiratory diseases limits the number of the sample to be included in this study.

CONCLUSIONS

- At therapeutic doses, 2mg / kg / day in 2 equally fixed divided doses before feeding for 24 weeks , propranolol is shown to be a safe and effective treatment of infantile hemangioma with significant improvement and low risk of the side effects in addition to no evidence of recurrence after cessation of treatment.
- Early treatment of hemangioma with propranolol is associated with significant clinical response and remarkable improvement in comparison with late one.
- Even in partially responding hemangioma, propranolol is found to accelerate healing of ulceration, thus reducing the ugly looking of infantile hemangioma, so achieving better satisfaction of the parents of the treated child.

RECOMMENDATION

- Based on its high efficacy, safety, low- risk profile and tolerance, we recommendpropranolol as a safe and effective first line therapy for infantile hemangiomairrespective of age, location, extent and phase of growth.
- Although with high level of safety profile of propranolol in pediatric population, but initial evaluation is recommended prior to the propranolol therapy to identify patients to whom the commencement of propranolol therapy may be carried a risk.
- As propranolol helps in downgrading the size and local complications of infantile hemangioma, we recommend propranolol prior to surgical intervention in order to make the lesion more amenable to be excised.
- Family education, regarding the proper dose, way of administration and early signs of propranolol side effects, is advisable.
- Further studies to clarify the factors influencing the response rate of infantile hemangima to oral propranolol therapy and the exact mode of action of propranolol in the healing of ulcerated hemangioma are recommended.

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