

Infantile Hemangioma Treatment with Topical and Systemic Beta-blockers, an Experience at Royal Medical Services Hospitals.

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ABSTRACT

Objective: Infantile hemangioma is the most common benign tumor in the neonatal age group.^(1,2) Which is characterized by rapid growth during the first several months of life, followed by slow spontaneous involution in the following years. Topical and systemic B-blocker therapy has been observed to stop rapid proliferation and accelerate regression of infantile hemangioma.^(1,2,3)

Methods: A simple statistical analysis was performed on patients who presented with infantile hemangioma and who were then treated with topical Timolol or oral Propranolol in our general dermatology clinics at Prince Hashem Hospital / Al-Zarqa and King Hussein Hospital /Amman, in the period between September 2015 and September 2017. Non of patients had received any prior treatment for the infantile hemangioma. Our Data include age, gender, site of hemangioma, treatment used, and duration of treatment, efficacy and adverse effects.

Results: 35 patients were diagnosed to have infantile hemangioma, Clinical diagnosis was made on all cases. Our sample had 27 female patients and 8 male patients. The mean age at presentation was 5.48 months. According to the location of the Infantile Hemangioma; 66% of patients had their lesions over head and neck, 20% of patients had lesions over extremities, and the remaining 14% had their lesions over trunk. 21 patients (60%) had mixed lesions with a superficial and deep components, 11 patients (31%) had superficial infantile hemangioma, 3 patients (9%) had deep lesions. 7 patients were treated with topical Timolol, for the mean duration of 7.4 months. Topical Timolol was given to 6 patients who had small superficial hemangiomas and 1 patient who had mixed component hemangioma, but for whom the parents refused the systemic Propranolol. The remaining 28 patients were treated with systemic Propranolol for the mean duration of 12.0 months. Systemic Propranolol was given for 27 patients who had mixed or deep hemangiomas and to 1 patient with superficial hemangioma over face. All patients showed almost complete clinical regression of the lesions with no recurrence, during the 6 months follow up period after stopping treatment. Propranolol treatment was discontinued in 3 patients due to respiratory events.

Conclusions: Topical Timolol and oral Propranolol are a very effective treatment for infantile hemangioma. Oral Propranolol can be safely initiated in an outpatient basis in infants older than 2 months of age.

Key words: B-blocker, Infantile Hemangioma (IH), Propranolol, Timolol.

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Introduction

Infantile hemangioma is the most common soft tissue tumor occurring in the early neonatal period, with a prevalence of approximately 5-10% of infants ^(1,3) Lesions are usually not present at birth and become evident during the first 4-6 weeks of life. IH is characterized by a rapid growth phase lasting from three to six months, then a period of stabilization for a few months , followed by a slow spontaneous involution over the next three to seven years. ^(4,5)

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During the involution phase, the lesions flatten, shrink and fade. The diagnosis of IH is usually clinical, imaging is not usually necessary, but Ultrasonography is the preferred initial modality if indicated. Although IHs are mostly asymptomatic, some may be associated with complications. Complications can include ulceration, bleeding, feeding problems, visual impairments, and permanent disfigurement with potential psychological effects on patient and parents^(6,7) Rarely IHs are associated with life threatening complications such as severe bleeding, respiratory obstruction, loss of vision, and heart or liver failure.⁽⁸⁾ Facial Hemangiomas are more complicated than non-facial Hemangioma.

Known risk factors for IH are low birth weight, female baby, caucasians, old mothers, multiple gestations and a history of prenatal complications as placenta previa and pre-eclampsia.^(4,9) The exact pathogenesis of IH is not well understood, IH may be derived from either: Vasculogenesis which is a de novo formation of vessels from progenitor stem cells or Angiogenesis which is a formation of new vessels from existing ones.^(1,2,10) Markers not expressed in normal tissue are frequently expressed in the endothelial cells of IH throughout both the rapid growth phase and the involution phase.^(10,11) Especially, vascular endothelial growth factor (VEGF), glucose transporter-1 (Glu T-1) and placenta associated vascular antigens i.e. Fc & RII, merosin, and Lewis Y antigen.⁽⁴⁾ The only other vascular tissue to share a similar expression profile of these markers is the placental chorionic villi.^(3,10) Unknown triggers by the second year of life stop the proliferation and accelerate apoptosis at which the involution phase starts.⁽¹²⁾ Potential molecular mediators of IH involution includes: increased quantities of mast cells, interferons induced gene and tissue metalloproteinase. And a decrease in fibroblast growth factor (FGF) level.^(13,14) Treatment of IH depends on the clinical picture and the severity of the lesion. As most lesions are small and uncomplicated with excellent prognosis for spontaneous resolution, these lesions are managed by active non-intervention (watchful waiting).^(4,8,15) However, intervention is required for IH that are causing functional impairment (such as impairment of vision, breathing or feeding), cosmetic impairment (as large facial lesions, lesions on lips, tip of the nose, genitalia and breast), or organ function impairment (liver failure or congestive heart failure).⁽¹⁶⁾

Systemic corticosteroids were the mainstay of treatment until 2008 when improvement with Beta-Blocker therapy was reported. Long term use of systemic corticosteroids resulted in significant adverse effects, including delayed growth, hypertension, cushingoid features, adrenocortical insufficiency and increased susceptibility to infections.^(3,5,17) Still Corticosteroids are considered as an alternative therapy if Propranolol cannot be used or is not effective.

In 2008 Leaute-Labreze et al made the major change in the treatment of IH, by observing the great improvement of lesions in patients being treated with the non-selective beta-blocker (Propranolol).^(6,7) The effect of Propranolol on IH is still not well known, however, it may induce microvascular vasoconstriction, inhibition of angiogenesis by down regulation of angiogenic factors such as vascular endothelial growth factor (VEGF), metalloproteinases, fibroblast growth factor (FGF) and early apoptosis of endothelial cells.^(3,18,19) B-Adrenergic receptors are expressed on endothelial cells of IH. They are more abundant in the proliferative phase of IH.^(1,3) Clinically B-blockers can induce a significant change in the color and consistency of the IH within the first few days or even hours after starting treatment.^(5,6,18) U.S. Food and Drug Administration has approved the oral Beta-blocker Propranolol for the treatment of IH.⁽⁴⁾

B-blockers especially Propranolol has been used since long time in the pediatric population for different conditions, such as in supra ventricular tachycardia, hyperthyroidism and arrhythmias. The doses range from 5-8 mg/kg/day. This has provided an excellent safety profile for this medication since long time.^(8,17) The dose used to treat IH is 1-3 mg/kg/day, for at least 6 months. it is a well tolerated dose with minimal side effects.^(2,3,20,21) The most common side effects include: sleep disturbances, acrocyanosis, hypotension, bradycardia and respiratory issues like infections, wheezing and stridor.^(6,20,22) The most significant side effects is the asymptomatic hypoglycemia. Sweating is the only early reliable sign of hypoglycemia that's not blocked by B-blockers.^(2,22) Hypoglycemia can be well controlled by frequent feeding, administration of the medication after feeding and avoidance of long time of sleeping.^(1,3)

Contraindications for Propranolol include: hypersensitivity to Propranolol, cardiogenic shock, documented chronic sinus bradycardia, documented chronic hypotension, first degree heart block, heart failure, history of bronchospasm or wheezing, preterm infants with corrected age less than 5 weeks and large facial hemangioma at risk for PHACES syndrome (Posterior fossa malformations, Hemangioma, Arterial abnormalities, Cardiac de-

fects, Eye abnormalities, Sternal defects and Supra umbilical raphia); since there is a potential risk for hypoperfusion of the brain.^(2,6,7,23)

Topical B-blocker, specifically Timolol maleate ophthalmic solution 0.5% is indicated for superficial or small IHs. ^(1,3,23)It is applied twice daily for the mean duration of 3-4 months.^(3,24) Timolol must be applied over intact skin overlying a hemangioma, not over ulcerated lesions or mucous membranes^(24,25). The exact level of systemic absorption is not yet known. Topical Timolol is 4-10 times more potent than Propranolol, and the topical absorption would bypass the first metabolism in the liver.⁽⁹⁾ Thus more caution must be considered with topical Timolol use until more information is available about its potential side effects.^(3,24)

Laser therapy may be useful in treating early lesions or residual telangiectasia. Resection of a proliferating IH generally is not recommended in infancy because younger patients have a higher risk of surgery complications. Delaying surgery until after infancy also allows for involution and better outcomes.

Methods

A simple statistical analysis was performed on patients with IH treated with topical Timolol or oral Propranolol at our general dermatology clinics, at Prince Hashem Hospital / Al-Zarqa and King Hussein Hospital / Amman, in the period between September 2015 and September 2017. Variables analyzed included age, gender, site of hemangioma, type of treatment used, and duration of treatment, efficacy and adverse effects. Diagnosis of all IH was done on clinical basis, except in 2 cases for whom US and MRI were done before being referred to the dermatology clinic. None of the patients had received any prior treatment for the infantile hemangioma. A thorough pretreatment assessment was performed by a general pediatrician that includes a detailed personal and family history and physical examination with particular focus on the respiratory and cardiovascular systems. Before initiation of treatment an electrocardiogram, blood pressure, heart rate monitoring and blood glucose level were done. The proper first dose of propranolol (2mg/kg/day, divided in 3 doses) was given in the clinic. Electrocardiogram, blood pressure, heart rate and blood glucose level were repeated one hour and two hours after treatment. A written hand out was given to parents including the exact dose, timing and the sign and symptoms of possible side effects. Patients were assessed 1,2,4 and 6 weeks after the first visit then every month after that, to evaluate response and satisfaction to treatment, to adjust the dose according to the new body weight and to check for the presence of any side effects. Criteria for response to treatment include a decreased color intensity and volume of the IH. Photos for all patients were taken with consent from parents.

Results

From 2015 to 2017, 35 patients with a diagnosis of IH were treated at our clinics. Our sample had 27 female patients and 8 male patients. The overall female to male ratio was 3.4:1. The mean age at time of presentation for all patients was 5.48 months, the range was (2-24 months), (See Table I). Single lesions were seen in 23 patients (67%) and multiple lesions in 12 patients (33%). The most common site for IH encountered was in the head and neck area, it seen in 23 patients (66%), seven patients (20%) had lesions on extremities, five patients (14%) had lesions on trunk.(See Table II).

Of our patients, 21 patients (60%) had mixed lesions with superficial and deep components, 11 patients (31%) had superficial infantile hemangioma, and three patients (9%) had deep lesions.

Seven patients with the mean age of 7.8 months were treated with twice daily application of topical Timolol ophthalmic solution 0.5%, for the mean duration of 7.4 months. Topical Timolol was given for 6 patients with small superficial hemangiomas and 1 patient with mixed component IH for whom the parents refused the systemic Propranolol.

28 patients with the mean age of 4.89 months were treated with systemic Propranolol, for the mean duration of 12.0 months. Propranolol was given to 27 patients who had mixed or deep hemangiomas and 1 patient with superficial hemangioma over the face upon this patient's request to administer systemic treatment. Propranolol was given at a dose of 2mg/kg/day, divided into 3 doses. (See Table III).

Three patients had respiratory side effects, in the form of recurrent attack of wheezy chest that led to discontinuation of treatment. Two of these patients had a partial response at time of discontinuation.

All patients showed almost complete clinical regression of the lesions with no recurrence, during the 6 months follow up period after stopping treatment. (See Figures 1, 2, 3, 4, 5)

Table I: Age, gender and number of patients.

Age (months)	Number of Female patients	Number of Male patients
0-3	8	3
4-6	13	2
7-12	6	2
13-18	—	—
19-24	—	1

Table II: Lesions location & Number of patients.

Site	Number of patients with single lesion	Number of patients with multiple lesions(<3)
Face	12	1
Scalp	8	2
Trunk	2	3
Extrimities	1	6

Table III: Duration & type of treatment used.

Duration of treatment (months)	Number of Timolol treated patients	Number of propranolol treated patients
<or =6	3	3
7-12	4	14
>12	-	11



Figure 1a:
4 months old female,
Mixed hemangioma with superficial & deep component over philtrum. Started topical Timolol Treatment.
(parents refused Propranolol)



Figure 1b:
13 months old.
After 9 months of timolol treatment.



Figure 2a:
2 months old female.
superficial hemangioma over face, close to medial aspect of lower
eye lid.
Started on Propranolol Treatment



Figure 2b
5 months old
(3 months on treatment)



Figure 2c:
18 months old.
16 months on Propranolol treatment



Figure 3a:
3 months old female .
Mixed hemangioma with superficial & deep component over scalp Started Propranolol treatment



Figure 3b:
6months old.



Figure 3c:
14 months old. After 11 months of Propranolol treatment.

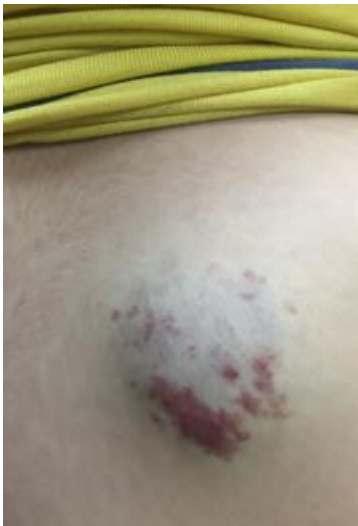


Figure 4a:
5 months old male.
Mixed hemangioma with deep & superficial components over back.
months after Propranolol treatment.
Started propranolol treatment.



Figure 4b:
16 months old.
11 months after propranolol treatment.



Figure 5a:
4 months old.
Superficial hemangioma over scalp, started on propranolol.



Figure 5b:
18 months old.
14 months on Propranolol treatment

Discussion

In our study, we dealt with 35 patients with IH; the aim of our treatment was to avoid the risk of permanent aesthetic disfigurement, to prevent organ dysfunction and to treat ulceration. None of our patients had a life threatening complications.

The female: male ratio was 3.4:1, which correlates with the published data about IH.^(4,8) 66% of our cases had IH lesions over head and neck, which is higher than the 50% reported in literature.^(4,9) The higher percentage that we had might be related to high parents concern about the cosmetic outcome of lesions over face, so they seek medical attention not like hemangioma else where over the body. 66% of our patients had single focal lesion which is very close to the published 67%.^(15,22) The mean age of starting treatment in our study was 5.48 months, which considered late depending on the published recommendation of starting treatment between 5 weeks and 5 months of age^(19,21,22,25), although some authors agree to start the treatment within the first 12 months of life.^(3,21) This late presentation could be due to late referral to dermatologist, which may be related to the insufficient awareness among general pediatricians about the efficacy and safety of Propranolol and Timolol. 60% of our patients had mixed lesions with superficial and deep component, though most articles describing IH showed that IH with mixed component not exceeding 35%^(4,9,15). This higher percentage that we had might be attributable to the loca-

tion of these mixed lesions, as most of them were located on the head and neck, which added to the cosmetic burden.

A consensus report recommends initiating Propranolol in a clinical setting with cardiovascular monitoring every hour for the first two hours, and repeated monitoring with dosage increases of more than 0.5 mg/Kg /day for infants older than eight weeks. In patient initiation should be considered for infants younger than eight weeks or with a post-conceptual age of less than 48 weeks and for infants with risk factors.^(3,6,12) The treatment duration for Propranolol mentioned in literature is 1 to 16 months.^(3,20,25) Although most authors used Propranolol for a period of 6 months,^(6,25) and Timolol for 3.4 months.^(3,24) We gave the treatment for a longer period of time; 12.0 months for Propranolol and 7.4 months for Timolol. We believe that the absence of rebound in our study group is related to the longer duration of treatment. As we didn't encounter any recurrence of IH over the six months follow up period.

The reported rebound growth after treatment discontinuation range from 17% to 19 %, ^(1,19,20) and might appear within 6 months after treatment discontinuation. ^(1,3,19)

The most common side effect encountered in our patients was bronchospasm and wheezy chest, which led to discontinuation of treatment in 3 patients. None of our patients reported an attack of irritability, sleep disorders, bradycardia, sweating, hypoglycemia or cold extremities. Although many articles didn't mention a serious adverse events that necessitate treatment discontinuation.^(19,20,28) Some articles reported that cardiac adverse effects followed by respiratory problems are the main causes to discontinue treatment.^(26,27)

The low percentage of reported side effects in our study group might be due to emphasis on the instructions given to the parents, absence of comorbidities and the close follow up offered to our patients.

Conclusion

IH cases are not uncommon in our general dermatology clinics. Topical Timolol and oral Propranolol are a very effective treatment for IH.

Oral Propranolol can be safely initiated in an outpatient basis in infants older than 2 months of age. The late presentation of our cases might be due to the late referral to dermatologist, which may be related to the insufficient awareness among physicians about the efficacy and safety of Propranolol as a treatment for IH.

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