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Original Research Article

PROPRANOLOL THERAPY IN INFANTILE HEMANGIOMAS

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Abstract

Background: Infantile hemangioma (IH) is the commonest vascular tumor affecting children that appears in the first 2 weeks of life and follows a proliferative phase that continues during the first year of life. After then, it undergoes involution, which lasts for several months or years depending on the size, site, gender, and development of complications. Report the long-term results of oral propranolol on congenital capillary hemangiomas in patients of treated in tertiary care hospital. **Materials and Methods:** Participants were treated with oral propranolol three times daily, with inpatient monitoring of adverse effects. The starting dosage was 2 mg/kg per day, which had been for the remaining duration of treatment. Therapy duration was planned for 4–6 months; if there was significant relapse, the period of treatment was extended. A photograph based severity scoring assessment was performed by three observers to evaluate efficacy by visual analog scale (VAS). **Result:** The female-to-male ratio was 4:1. The median age at start of treatment with propranolol was 3.4 (0.6–10.2)) months. All patients were treated with propranolol at a dose of 2 mg/kg per day. All patients completed treatment at median age of 10.1 (8.2–18.2) months and after a median treatment duration of 8.6 (4.4–16) months. The median follow-up-time of all patients was 15 (6–20) months. No severe adverse events were noted in our patients. 10 (25 %) showed a reaction possibly due to the medication. In all patients, there was significant fading of color [with a VAS of -9(-6to-9) after 6 months] and significant decrease in size of the infantile hemangiomas [with a VAS of -8(-3to-10) after 6 months]. **Conclusion:** Propranolol has been shown to be safe and a promising therapeutic option in the treatment of cutaneous IHs. It has mild tolerable side effect with the dose used in this study and very few complications.

INTRODUCTION

Infantile haemangiomas (IHs) are the most common benign tumour in pediatric patients, and 60% of IHs occur on the head and neck. IHs usually manifest during the 1st month of life and the proliferative phase extends for the first 2 years of age.[1,2] These haemangiomas may be disfiguring but are not usually life-threatening or function impairing, and most clinicians emphasize an approach of observation before any intervention. Most IHs involute spontaneously in the first decade of life after the 2nd year. However, a subset of IHs does not involute spontaneously and this may lead to serious complications and cosmetic disfigurement, and thereby functional and psychological effects on parents and the affected children.[2] Although several treatment modalities have been used in the past; propranolol, a β-blocker, has been proven to be very effective and safe for IHs therapy, and has replaced corticosteroids as the first-line treatment for IHs.[3] The mechanism of action of propranolol is not established yet but may involve microvascular vasoconstriction and modulation of angiotensin II.[4] Alterations in the cell signalling of angiogenic factors and early apoptosis of endothelial cells may also be involved.[5] In this study, our objective is to study the efficacy of propranolol in different subsets of children in our population with IHs and to analyse factors affecting the clinical outcome.

MATERIALS AND METHODS

We describe 50 infants with congenital capillary hemangiomas who received treatment from the age of 3-4 months up to the end of the first year of life.

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The study was approved by the Ethics Committee. Informed consent was obtained from the patients' guardians prior to the study. All patients were admitted and monitored for 3 days, and underwent a complete baseline ophthalmic examination. Laboratory studies including complete blood count, blood urea nitrogen (BUN), serum creatinine, blood sugar, sodium and potassium levels were performed at the beginning of the study.

Treatment was initiated at a dose of 1mg/kg/day propranolol solution (Inderal 20mg/5ml) on the first day; if vital signs and blood sugar were stable the dose was doubled on the following day. The maintenance dose was 1-2mg/kg/day divided in two doses. Patients were fed 2 to 3 hours after administration of propranolol. They were followed twice a week for 2 months and then monthly for 20 months. If no further benefit was observed during follow-up, propranolol was tapered over 2-3 weeks.

Follow-up visits were scheduled monthly and at any time in case of complications. The dosage of propranolol was adjusted to the weight of the patient only in case of relapse of the hemangioma or a stop in regression after an initially observed decrease. At each clinic visit, blood pressure, heart rate, and blood glucose was measured, the effect of the treatment were determined, and possible adverse events were documented. We obtained serial clinical images to assess the rate and degree of recurrence. A visual scale to assess the severity of the IH was used. Briefly, three of the authors independently evaluated clinical images taken at baseline and in the follow-up visits. The observer documented changes in color and size of the lesions on a visual analog scale (VAS) ranging from −10 to +10 by comparing follow-up images to the baseline photograph pretreatment. On the VAS 0 represented the baseline photograph (pre-treatment), a decrease in color or size resulted in a − number, an increase in color or size in a + number.

Statistical Analysis

Data collected from the patients' charts, ultrasound examination, and evaluation of photographs by VAS were entered into a computerized database. Median and range were calculated for continuos values. The Wilcoxon test was used to compare two related samples and the null hypothesis was rejected with a two-sided p value of <0.05.

RESULTS

50 patients with IH were included in the study. The relevant epidemiologic and clinical characteristics of the patients and details about the individual treatment indication and duration.

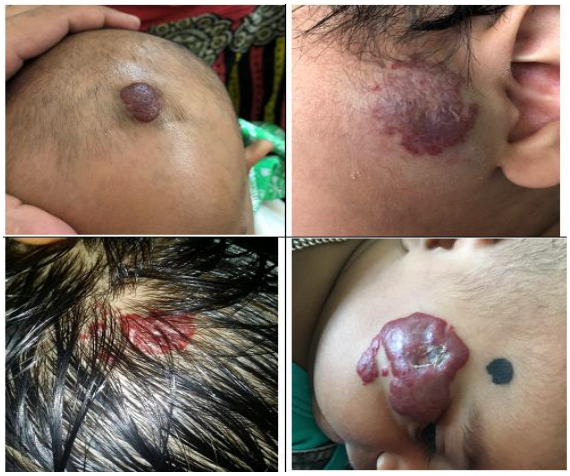

Figure 1: Congenital capillary hemangiomas in present study

Table 1: Baseline characteristics and treatment of infantile hemangiomas

Patient characteristics and treatment	**n = 50**
Female-to-male ratio	40:10
Type of hemangioma	
Superficial	20
Deep	18
Mix	12
Location of hemangioma	
Head	6
Nose	11
Mouth	15
Periocular	4
Parotid area	2
Trunk	2
Limbs	4
Ulcerated hemangiomas	1
Age initiation of propranolol (months) median (range)	3.4 (0.6–10.2)
Duration of propranolol treatment (months), median (range)	8.6 (4.4–16)
Age at end of propranolol treatment (months), median (range)	10.1 (8.2–18.2)
Duration of propranolol treatment until stopped, median (range)	8.6 (4.4–16)

The female-to-male ratio was 4:1. The median age at start of treatment with propranolol was 3.4 (0.6–10.2)) months. All patients were treated with propranolol at a dose of 2 mg/kg per day. All patients completed treatment at median age of 10.1 (8.2–18.2) months and after a median treatment duration of 8.6 (4.4–16) months. The median follow-up-time of all patients was 15 (6–20) months.

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Table 2: Complications and adverse effects

Observed adverse effects	n (%)	Propranolol terminated because adverse effects, n
Hypoglycemia	0	0
Hypotension	0	0
Bradycardia	1	0
Seizure	0	0
Restless sleep	2	0
Cold extremities	1	0
Gastrointestinal problems	5	0
Diarrhea	4	
Constipation	2	
Bronchial asthma	1	1

No severe adverse events were noted in our patients. 10 (25 %) showed a reaction possibly due to the medication. Therapy was interrupted in one child who had temporary aggravation of preexisting asthma. All other observed adverse effects were mild and were tolerated without discontinuing the medication.

Changes of VAS regarding color (a) and size (b) of the hemangiomas during follow-up and treatment with propranolol (BL baseline, d days, m months); $p < 0.01$ for both parameters.

Table 3: Visual scale scoring as evaluated three independent observers

Case location	Mean ± standard deviation			Recurring component	Segmental of focal	Retreatment
	Age before propranolol months	Age at propranolol termination months	Age at maximal recurrence months			
Left chest	10 ± 1.5	1.7 ± 11	8.52 ± 15	Superficial and deep	Focal	Yes, good response
Upper lip	9 ± 3	3.54 ± 9	6.32 ± 15	Deep	Segmental	Yes, good response
Right arm	9 ± 7	0 ± 13	5 ± 21	Deep	Focal	No

3 cases have recurrence in which did not respond of which on retreatment 2 cases responded.

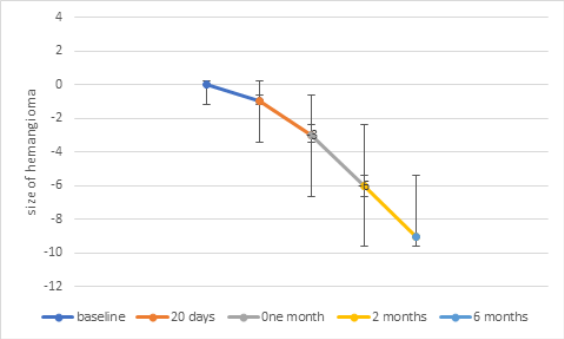

Figure 2: size of the infantile hemangiomas in correlation with age

In all patients, there was significant fading of color [with a VAS of -9(-6to-9) after 6 months] and significant decrease in size of the infantile hemangiomas [with a VAS of -8(-3to-10) after 6 months].

DISCUSSION

After the serendipitous discovery of propranolol for the treatment of IHs,[5] a nonselective β-blocker used to treat hypertension, tachycardia, heart failure, and acute myocardial infarction, numerous reports around the world have described satisfactory responses.[6-8] Before that systemic corticosteroids have been the mainstay of therapy for treatment of IHs.[9] Even though propranolol has become an attractive therapeutic alternative, there is no universally accepted protocol with propranolol or its dosing, and we have sparse literature about its safety and efficacy in the Indian population, especially infants. Through this work, we have endeavored to clarify certain aspects on its safety profile and end point of therapy, using a combination of subjective and objective outcome parameters to reduce biases.

The doses used in pediatric patients for this indication have ranged between 0.5 and 6 mg/kg/day.[10] In a meta-analysis by Marqueling et al. involving 41 studies of ≥1200 children treated with propranolol, with a mean dose of 2.1 mg/kg/day and treatment duration of 6.4 months, a response rate of 98% was noted. Serious side effects were rare, occurring in <1% of patients.[11] Consistent with these studies, we chose to use 2 mg/kg/day as the regular dose, with 1 mg/kg/day as the initiating dose in all age groups. With this dosing range, propranolol has been safe and effective in our population.

The clinical and demographic characteristic of our patients were mostly in agreement with those previously described in the literature, Although we had a mean duration of therapy as 8.6 months here, a consensus on the ideal duration of treatment required is not established. The authors have variably suggested to continue propranolol for 6 months duration, for at least the 1st year of life when the proliferation phase is mostly over, to complete resolution of the lesion.[12]

We did not observe any severe adverse effects, although there have been a few reports of serious adverse effects, particularly hypoglycemia. Adverse

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effects of beta-blockers for other medical indications have also been reported, including hypotension, bradycardia, bronchospasm, and hypoglycemia. Non-selective beta-blockers are
competitive antagonists of catecholamines at the b-1 and b-2 adrenergic receptors. Beta-2 receptor blockade may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis, and lipolysis. Lawley et al,[13] reported the cases of two patients who received propranolol in the recommended dosage of 2 mg/kg per day. One experienced severe hypotension and the other severe hypoglycemia. Other authors have reported similar cases.[14,15] Burns et al,[16] stated that hypoglycemia can be associated with poor neurological outcome. Symptomatic hypoglycaemia can be a serious complication of propranolol treatment. A propranolol dosage of over 4 mg/kg per day seems to put the pediatric patient at risk for development of hypoglycemic events.[17] Propranolol had to be discontinued in one patient because of bronchial hyperreactivity during viral infections. Bronchial hyperreactivity is a direct effect of non-beta-selectivity of propranolol, resulting in bronchospasm due to pulmonic beta-2-blockade. The use of a non-selective lipophilic beta-blocker results in several other reported side effects. Restless sleep is probably a direct result of the lipophilic character of propranolol, which allows it to cross the blood brain barrier. A solution to many of the side effects of propranolol therapy may be the use of more selective b-1 antagonists such as metoprolol, which, at low dosage, have little b-2 activity; thus, in theory they bear a lower risk of inducing hypoglycaemia and bronchospasm. Treatment with a hydrophilic beta-1 antagonist such as atenolol may prevent side effects, such as restless sleep. However, it is not yet known if these selective beta-blockers will have efficacy that is equal to propranolol. Our study confirms the impressive results of propranolol as a treatment for IH. It seems to be a more effective and safer therapeutic drug than systemic corticosteroids. Its use may be expanded to treatment of IH after the first year of life. Because of potentially harmful side effects, including hypoglycemia, bronchospasm, and hypotension, these patients is preferably treated in a multidisciplinary setting by physicians knowledgeable about the effects and side-effects of propranolol.

We confirmed that IH successfully treated with propranolol may recur 0–6 months after therapy withdrawal. The rate of clinically visible recurrence of IH in our series of 50 patients was 6 %, suggesting that 3 cases propranolol does not result in permanent shrinkage. The frequency of recurrences in patients treated with propranolol has not been well-characterized. In the series of cases reported by Sans et al,[18] 2 of 25 patients (8 %) had recurrences after treatment withdrawal. The overall response to retreatment with propranolol was satisfactory. These relapses occurred before the age of 11 months, which might mean that the treatment was with- drawn before the proliferative phase of the IH was over.[18]

Hemangioma recurrence is also often seen in patients treated with corticosteroids. Although a comparison of the two treatments is not possible, it is the authors' impression that the rate of recurrence is lower with propranolol than with corticosteroids. The main proposed mechanisms involved in the effectiveness of propranolol for IH include vasoconstriction, inhibition of angiogenesis, inhibition of the renin–angiotensin system, and induction of apoptosis.[19] Apoptosis of endothelial cells in the hemangioma is supposed to be the most likely mechanism involved in its natural involution, and propranolol has been proved to induce apoptosis of such hemangioma cells. As suggested, apoptosis may not be complete in all cases after treatment withdrawal, and thus some endothelial cells may remain proliferative after treatment is stopped.[18] It is unknown why other IH, showing only partial response to propranolol, do not experience further proliferation of the remaining endothelial cells after propranolol withdrawal.

CONCLUSION

In conclusion, Propranolol has been shown to be safe and a promising therapeutic option in the treatment of cutaneous IHs. It has mild tolerable side effect with the dose used in this study and very few complications. Although we observed a recurrence rate of 6 % of cases of IH treated with propranolol after withdrawal. In all, propranolol appears to be an effective treatment for infantile hamangiomas and should now be used as a first-line treatment in hemangiomas when intervention is required. Also, further studies should be needed in determining the most effective treatment dosage, optimum treatment duration, and exact mechanism of action of propranolol in future.

REFERENCES

1. Léauté-Labrèze C, Voisard JJ, Moore N. Oral propranolol for infantile hemangioma. N Engl J Med. 2015;16:284–5.
2. Talaat AA, Elbasiouny MS, Elgendy DS, Elwakil TF. Propranolol treatment of infantile hemangioma: Clinical and radiologic evaluations. J Pediatr Surg. 2012;47:707–14.
3. MacIsaac ZM, Nayar HS, Gehris R, Mehta D, Geisler S, Grunwaldt LJ, et al. Treatment for infantile hemangiomas: Selection criteria, safety, and outcomes using oral propranolol during the early phase of propranolol use for hemangiomas. J Craniofac Surg. 2016;27:159–62.
4. Itinteang T, Brasch HD, Tan ST, Day DJ. Expression of components of the renin-angiotensin system in proliferating infantile haemangioma may account for the propranolol-induced accelerated involution. J Plast Reconstr Aesthet Surg. 2011;64:759–65.
5. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: Part II. Risks, complications and treatment. J Eur Acad Dermatol Venereol. 2011;25:1254–60.
6. Lawley LP, Siegfried E, Todd JL. Propranolol treatment for hemangioma of infancy: Risks and recommendations. Pediatr Dermatol. 2009;26:610–4.
7. Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: An update on pathogenesis and therapy. Pediatrics. 2013;131:99–108.

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8. Schupp CJ, Kleber JB, Günther P, Holland-Cunz S. Propranolol therapy in 55 infants with infantile hemangioma: Dosage, duration, adverse effects, and outcome. Pediatr Dermatol. 2011;28:640–4.
9. Rössler J, Wehl G, Niemeyer CM. Evaluating systemic prednisone therapy for proliferating haemangioma in infancy. Eur J Pediatr. 2008;167:813–5.
10. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011;128:e259–66.
11. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol for Infantile Hemangiomas: A Meta Analysis. Monterey, CA: Poster at the Society for Pediatric Dermatology Annual Meeting; 2012. Jul,
12. Hsu TC, Wang JD, Chen CH, Chang TK, Wang TM, Chou CM, et al. Treatment with propranolol for infantile hemangioma in 13 Taiwanese newborns and young infants. Pediatr Neonatol. 2012;53:125–32.
13. Lawley LP, Siegfried E, Todd JL. Propranolol treatment for hemangioma of infancy: risks and recommendations. Pediatr Dermatol. 2009;26:610–614. doi: 10.1111/j.1525-1470.2009.00975.x.
14. Manunza F, Syed S, Laguda B, Linward J, Kennedy H, Gholam K, et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. Br J Dermatol. 2010;162:466–468.
15. Siegfried EC, Keenan WJ, Al-Jureidini S. More on propranolol for haemangiomas of infancy. N Engl J Med. 2008;359:2846–2847.
16. Burns CM, Rutherford MA, Boardman JP, et al. Patterns of cerebral injury and neuropathologic outcomes after symptomatic neonatal hypoglycaemia. Pediatr. 2008;122:65–74.
17. Chavez H, Ozolins D, Losek JD. Hypoglycemia and propranolol in pediatric behavioral disorders. Pediatrics. 1999;103:1290–1292.
18. Sans V, Dumas de la Roque E, Berge J, et al. Propranolol for severe infantile hemangiomas: follow up-report. Pediatrics. 2009;124:423–431.
19. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol. 2010;163:269–274.

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