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To study the role of propranolol in infantile hemangioma: A prospective randomized study

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ABSTRACT

Background: Infantile capillary hemangiomas (IHs) are common, benign, self-limited tumors with a well-defined natural history, occurring most often on the head and neck. IHs are the most common soft-tissue tumors in infancy and occur in 5–10% of children. The main risk factors identified for IH include female sex and low birth weight. For many hemangioma patients, treatment is not required; however, there are many treatment options for IH, each with their own limitations and side effects. **Aims and Objectives:** The study aimed to study the role, efficacy, and side effects of propranolol in infantile hemangioma. **Materials and Methods:** Patients with infantile hemangioma at SN Medical College, Agra, in the Department of General Surgery and Pediatric Surgery with the required eligibility criteria are considered in this study from December 2021 to December 2023, in total 60 patients, prospectively randomized into three groups: Group A: Infants given propranolol only. Group B: Infants given steroids only Group C: Infants given a steroid plus propranolol. **Results:** In our study, Group A taking propranolol alone 14 out of 20 (70%) responded well, Group B taking steroid alone 7 out of 20 (35%) responded well and Group C taking steroid and propranolol 16 out of 20 (80%) responded well, which shows that propranolol in a low dose (0.5–3 mg/kg/day) is an effective drug for infantile hemangioma. **Conclusion:** In our study, we can conclude that propranolol is a safe, efficacious, and better drug than corticosteroid for infantile hemangioma when used in low doses, and the effects are better if started in the early phase.

Key words: Infentile hemangioma; Proprenolol; Lesions

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INTRODUCTION

Hemangiomas are clonal expansions of endothelial cells and are the benign vascular neoplasm[1] and most common tumors of infancy that have a characteristics clinical course marked by rapid growth, followed by slower growth, and gradual involution. Infantile capillary hemangioma (sometime called a strawberry birthmark) affect 4–10% of infants,[2] Infantile hemangiomas in general can occur at any site of the body, including the vital organs such as face and genitalia, and can result in complications such as cosmetic disfigurement and anatomical obstruction. The first sign of infantile hemangiomas is characteristically an area of pallor that appears several days after birth. The usual size is 0.5–5 cm and is usually circumscribed and focal. Rapid growth during the first 4 weeks of life is the historical hallmark. Most growth occurs during the first 4–6 months of life. Infantile capillary hemangiomas are common, benign, self-limited tumors[3] with a well-defined natural history, occurring most often on the head and neck. The usual diagnosis is by taking a natural history and by clinical examination. Treatment modalities vary depending on the extent and location of the lesion. For many hemangiomas, treatment is not required; however, hemangiomas in some locations need treatment to prevent complications (10–15% IH-caused complications) such as disruption to visual pathways, risk to the airway or feeding, ulceration, or poor cosmetic outcome.[4] There are many treatment options for IH, each with their own limitations and side effects. The traditional treatment options include corticosteroids systemically, by local injection and topical application, interferon, laser, and surgical resection. Each

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treatment option has limited therapeutic benefit, with its own side effects and risks; however, in the past 3 years, there have been more than 120 reports of the efficacy of oral beta-blockers as a highly effective therapeutic option for IH and its complications.[5] Systemic treatment with propranolol is quickly becoming the standard of care worldwide and the first-line agent due to its safety and efficacy.[6] It is considered for rapidly enlarging or large IHs that are vision- or life-threatening, such as perioral hemangiomas causing feeding or breathing difficulty. Propranolol is a medicine from the class of beta-blockers. It acts by inhibiting the growth of blood vessels and by constricting existing blood vessels within the hemangioma. It acts by decreasing the release of vascular endothelial growth factor and basic fibroblast growth factor and by triggering programed cell death.[7,8]

Aims and objectives

The study aimed to study the role of propranolol in infantile hemangioma: a prospective randomized study.

1. To study the efficacy of oral propranolol in infantile capillary hemangiomas
2. To compare propranolol with oral steroids for the treatment of IFH
3. To study the possible adverse effects of propranolol therapy
4. To determine the treatment protocol for dosage and duration of treatment with oral propranolol in infantile capillary hemangiomas.

MATERIALS AND METHODS

Patients with infantile hemangioma at SN Medical College, Agra, in the Department of General Surgery and Pediatric Surgery, a total of 60 patients with the required eligibility criteria, were considered in this study from December 2021 to December 2023.

Eligibility criteria

All patients with proven capillary hemangioma are included in the study. These patients undergo thorough clinical, general, and systemic examinations and the required investigational procedures.

Inclusion criteria

All patients up to 1 year of age with proven infantile capillary hemangioma must have the consent of their guardians.

Exclusion criteria

Subjects with underlying AV malformation, subjects with associated cardiac conditions or bronchial asthma, a known coagulopathy or hematological disorder, any patient not giving consent, and known case of pheochromocytoma were excluded from the study.

Method

We developed a treatment protocol to optimize safety. Medication is given every 8 hourly with an initial dose of 0.5–1 mg/kg body weight/day, increasing to 3 mg/kg/day in 3 divided doses. Follow-up consisted of monthly clinic visits to access therapy progress and eventual dose adjustments. Propranolol is gradually tapered over a period of 2 weeks. Hemangiomas undergoing propranolol therapy are photographed in series before and during their treatment cycles to document treatment responses. Parents were asked to tell us about any side effects of the treatment and their overall satisfaction with the propranolol treatment. The patients were prospectively randomized into three groups: Group A: Infants given propranolol only. Group B: Infants given steroid only. Group C: Infants given a steroid plus propranolol. Results are based on the degree of response to treatment: (1) those who respond >75% (responders), and (2) those who respond <75% (non-responders). Response is calculated as total volume regression in terms of length, breath, and depth as estimated by clinical examination and ultrasound.

Observation

A total of around 60 patients were studied during the time period from December 2021 to December 2023, after ethical clearance from the ethical committee and with the proper consent of the patient's guardians. All the patients were either admitted or referred to the Department of General Surgery and the department of Pediatric surgery at SN Medical College, Agra. The following observations were made on the basis of the study: the sex distribution of the study group female 36 patients (60%) and male 24 patients (40%). Patients were brought to us with the following complaints: dark discoloration (40), localized swelling or lump (54), cosmetic disfigurement (26), and hemangioma over vital organs like the face, airway, genitalia, etc. (13). A total of 60 patients were studied. Patients were randomly divided into three groups of 20 each. Each group was given either propranolol, steroid, or steroid plus propranolol. And the effects were studied, and the patients were followed for any recurrence or complications. The dose of propranolol was 0.5–3 mg/kg/day in divided doses, and the dose of steroid was 5 mg/kg/day. Propranolol was started at a dose of 0.5 mg/kg/day, then the patients were monitored for the possible side effects of bradycardia, hypotension, and respiratory distress. If the patient was stable, the dose was gradually increased to two and then three if the patient could tolerate it, then continued for a period of around 9–12 months, then gradually tapered so as to prevent rebound of the lesion size.

In our study, Group A patients (20) was given Propranolol; 14 patients (70%) were responders, while Group B patients

(20) were given steroids, 7 patients (35%) were responders, and if patients were given propranolol+steroid in Group C (20),\\\ 16 patients (80%) were responders.

We observed that results are best when started in 1–3-month-old patients. Hence, our study concluded that earlier we started the therapy, the results were better. Results are good with patients given beta-blockers (proprenolol) only and best with patients given beta-blocker+steroid combination.

Data were compiled, and analysis was performed using STATA software version 11.0. The statistical tests applied were the chi-square test and the Wilcoxon signed rank test. The P-value was calculated using the Fisher's exact test owing to the small sample size, and a value <0.05 was considered to be statistically significant. The P-value is significant in groups A (0.04) and C (P=0.03) which shows that propranolol alone or in combination with steroids is an effective treatment for IH. But in group C, side effects related to steroids are present, while in group A, there are minimum and controllable side effects. During the therapy with propranolol, patients were monitored for the possible side effects of bronchospasm (respiratory efforts and saturation), bradycardia, and hypoglycemia. Hypoglycemia is a common side effect noted in infants, which is why it is given along with the feds. Due to the side effects of beta blockers, 4 patients left the course in between the studies. The patients in whom side effects were observed responded well when the treatment was stopped without any significant morbidity. Patients were treated until the age of 1 year, after which the drug was tapered over the time period of two weeks, and the patients were monitored for recurrence or relapse of the lesion.

RESULTS

In our study, Group A taking propranolol alone 14 out of 20 (70%) responded well, Group B taking steroid alone 7 out of 20 (35%) responded well, and Group C taking steroid and propranolol 16 out of 20 (80%) (Tables 1-3) responded well which shows that propranolol in a low dose (0.5–3 mg/kg/day) is an effective drug for infantile hemangioma (P=0.04) with minimum or no side effects and is a better drug than corticosteroids (P=0.06) with the most common side effects noted being bradycardia, hypotension, and hypoglycemia (Tables 4 and 5).

DISCUSSION

Capillary hemangiomas are common childhood tumors, reaching their maximum growth in the 1st year of life.

Table 1: Responses to beta-blocker (propranolol), steroid, and propranolol+steroid

Drug given	Total patient	Responders* (%)
Beta-blocker	20	14 (70)
Steroid	20	7 (35)
Beta-Blocker+Steroid	20	16 (80)

*Responder- Those patients whose lesion size decrease by>75%, Non-responder- Those patients whose lesion size either did not decrease or decreased <75%

Complete spontaneous regression of the tumor occurs in 32–60% of patients by the age of four and in 72–76% by the age of 7 years. In addition, massive hemangiomas alter skin structure by stretching or injury to the surface texture and may cause disfigurement.[9,10] There are some reports on the dramatic effect of oral propranolol on the size and volume of vascular masses, which were replicated in our patients as well. It is interesting that the first visible and measurable response to treatment was observed within 48 h of initiating treatment in superficial cases. The lesion size decreased to half its original size after 2 months. This rapid response, as compared to corticosteroid-based treatments, is especially valuable. Bradycardia, hypoglycemia, and hypotension are the most common side effects of propranolol.[11] History of pre-maturity, age <3 months, comorbidities, and asthma are factors associated with a higher risk of side effects. During the follow-up period and after discontinuation of treatment, we observed no complications, tumor regrowth, or general growth impairment in our cases. Compared to other published reports on the treatment of capillary hemangiomas with propranolol, our cases had a longer duration of follow-up. Based on the good results and a low risk profile, we recommend propranolol as a safe and effective first-line therapy for capillary hemangiomas in children. In our study among Group A: 14 patients responded well from total of 20 patients (70%). Out of these 14 responder patients 10 (71.43%) are female and 4 are male (66.66%); P=0.043, among Group B: seven patients responded well from total of 20 patients (35%) out of these 3 (30%) responders are male and 4 (40%) responders are female; P=0.063, among group C: 16 patients responded well from total of 20 patients (80%) Out of these 5 (62.5%) responders are male and 11 (91.67%) responders are female; P=0.031. Our study corresponds to the study done by Marquelling et al.,[12] and Shah et al.,[13] about the superiority of propranolol over corticosteroids in the treatment of IH. In terms of the side effects profile, our study is consistent with that done by Labreze et al.,[8] about the risk-to-benefit ratio of propranolol.

Limitations of the study

The limitation of the study is low number of patients included in the study and poor follow-up.

Table 2: Age wise distribution of response to propranolol (beta-blocker) alone, steroid alone and propranolol+steroid.

Age group	Beta-blocker alone		Steroids alone		Beta-Blocker+Steroids	
	Number of patients	Responder (%)	Number of patients	Responder (%)	Number of patients	Responder (%)
1–3 Months	5	5 (100)	5	3 (60)	5	5 (100)
3–6 Months	5	3 (60)	5	2 (40)	5	4 (80)
6–9 Months	5	3 (60)	5	1 (20)	5	3 (60)
9–12 Months	5	3 (60)	5	1 (20)	5	4 (80)

Results are bests when started the treatment in 1-3 months age group patients.

Table 3: Distribution of lesions on the basis of age of presentation in weeks, area of lesion in square cm and the duration of therapy in weeks

Sex (No. of cases)	Group A Propranolol (n=20)		Group B Steroid (n=20)		Group C Propranolol+Steroid (n=20)		Total
	Female	Male	Female	Male	Female	Male	
	14	6	10	10	12	8	60
Age of presentation (weeks)	17±3.4	14±3.2	16±2.7	14±2.9	19±3.3	15±2.8	15.83±3.05
Area of lesion (square cm)	28±5.5	27±4.8	25±3.7	23±3.5	24±4.9	25±4.7	25.33±4.51
Duration of therapy (weeks)	18.5±4.3	17.9±2.8	17.8±3.1	18.3±2.8	18.6±4.2	18.2±5.5	18.22±3.78

Table 4: Sex-wise distribution of response following treatment in various groups (n=60)

Groups	Sex	Non-responder (<75%)	Responders (>75%)	P-values
Group A (Propranolol alone)	Female	4	10	0.0431 (P<0.05)
	Male	2	4	
Group B (Steroid alone)	Female	6	4	0.06392
	Male	7	3	
Group C (Propranolol+Steroid)	Female	1	11	0.03101 (P<0.05)
	Male	3	5	
Total		23	37	

*P<0.05 statistically significant

Table 5: Adverse drug reactions

Adverse drug reactions Noted	Propranolol (n_1=20)	Steroid (n_2=20)	Steroid plus propranolol (n_3=20)
1. Bradycardia	2	0	0
2. Hypotension	1	0	0
3. Hypoglycemia	3	0	0
4. Hypersomnolescence	0	0	0
5. Cardiomyopathy	0	3	3
6. Generalized Body Edema	0	1	2
7. Mortality	0	0	0

CONCLUSION

Hence, from our study, we can conclude that propranolol is a safe, efficacious, and better drug than corticosteroids for infantile hemangioma when used in low doses, and the effects are better if started in the early phase.

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REFERENCES

1. Kilcline C and Frieden IJ. Infantile hemangiomas: How common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168-173.
https://doi.org/10.1111/j.1525-1470.2008.00626.x
2. Hoornweg MJ, Smeulders MJ, Ubbink DT and Van der Horst CM. The prevalence and risk factors of infantile haemangiomas: A case-control study in the Dutch population. Paediatr Perinat Epidemiol. 2012;26(2):156-162.
https://doi.org/10.1111/j.1365-3016.2011.01214.x
3. Metry DW and Hebert AA. Benign cutaneous vascular tumors of infancy: When to worry, what to do. Arch Dermatol.

2000;136(7):905-914.
https://doi.org/10.1001/archderm.136.7.905

4. Leaute-Labreze C, Boccara O, Degrugillier-Chopinet C, Mazereeuw-Hautier J, Prey S, Lebbe G, et al. Safety of oral propranolol for the treatment of infantile hemangioma: A systematic review. Pediatrics. 2016;138(4):e20160353.
https://doi.org/10.1542/peds.2016-0353
5. Sans V, De la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, et al. Propranolol for severe infantile hemangiomas: Follow-up report. Pediatrics. 2009;124(3):423-431.
https://doi.org/10.1542/peds.2008-3458
6. Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, et al. Propranolol vs corticosteroids for infantile hemangiomas: A multicenter retrospective analysis. Arch Dermatol. 2011;147(12):1371-1376.
https://doi.org/10.1001/archdermatol.2011.203
7. Leaute-Labze C and Taieb A. Efficacy of beta-blockers in infantile capillary haemangiomas: The physiopathological significance and therapeutic consequences. Ann Dermatol Venereol. 2008;135(12):860-862.
https://doi.org/10.1016/j.annder.2008.10.006
8. Léauté-Labrèze C, De La Roque ED, Hubiche T, Boralevi F, Thambo JB and Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649-2651.
https://doi.org/10.1056/NEJMc0708819
9. Tan ST, Itinteang T and Leadbitter P. Low-dose propranolol for infantile haemangioma. J Plast Reconstr Aesthet Surg. 2011;64(3):292-299.
https://doi.org/10.1016/j.bjps.2010.06.010
10. Arneja JS, Pappas PN, Shwayder TA, Cullen ML, Becker CJ, Hamzavi FH, et al. Management of complicated facial hemangiomas with beta-blocker (propranolol) therapy. Plast Reconstr Surg. 2010;126(3):889-895.
https://doi.org/10.1097/PRS.0b013e3181e5f8b6
11. Holland KE and Drolet BA. Infantile hemangioma. Pediatr Clin North Am. 2010;57(5):1069-1083.
https://doi.org/10.1016/j.pcl.2010.07.008
12. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: A systematic review. Pediatr Dermatol. 2013;30:182–91.
13. Shah MK, Vasani RJ. Use of propranolol in infantile hemangioma. Indian J Drugs Dermatol 2017;3:48-52.

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