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Original research article

Role of propranolol in the management strategies of infantile hemangioma from a tertiary care hospital

[1]Dr. Venkataramana G, [2]Dr. Malle Nagaveni, [3]Dr. Bhanu Prakash Goud, [4]Dr. Srinivas

[1, 4]Assistant Professor, Department of General Surgery, Navodaya Medical College Hospital and Research Centre, Mantralayam Road, Raichur, Karnataka, India

[2]Assistant Professor, Department of Pediatrics, Navodaya Medical College Hospital and Research Centre, Mantralayam Road, Raichur, Karnataka, India

[3]Assistant Professor, Department of Pharmacology, Kurnool Medical College, Kurnool, India

Corresponding Author:
Dr. Malle Nagaveni

Abstract

Aims and Objectives: To study the impact of propranolol in the management of Infantile Hemangiomas.

Methods: This prospective study was conducted in Department of Pediatrics, Navodaya Medical College Hospital and Research Centre, Mantralayam Road, Raichur, Karnataka, India over a period April 2021 to March 2022. All children with hemangiomas attending in hospital outpatient department during the study period.

Results: The mean duration of propranolol therapy for superficial and deep hemangiomas was 8.96 months and 8.8 months respectively. For the hemangiomas in the head region, the mean duration of propranolol therapy was 9.72months and for the hemangiomas in the trunk and the extremities it was 8.6 and 10.5 months respectively.

Conclusion: All children tolerated propranolol well without significant side effects. No one had required interruption or withdrawal of propranolol therapy for side effects.

Keywords: Propranolol, female, hemangiomas, proptosis, prospective study

Introduction

A benign vascular proliferation, infantile hemangiomas (IH) are the most prevalent tumor of infancy and affect 5–10% of people [1]. Compared to Caucasian children, they are more frequently seen in females and less frequently in Asian and African American children [2-4]. The most frequently affected area is the head and neck region, which accounts for 60% of cases, followed by the trunk (25%) and extremities (15%) [2-4].

There is a predictable natural history for infantile hemangiomas [5]. Some may have a precursor lesion, such as a vascular patch or an area of pallor, even though the majority are not present at birth. Infantile hemangiomas experience significant growth shortly after birth (proliferative phase) for several months, followed by gradual involution that typically takes place over several years. The periorbital area, central face, airway, skin folds, and anogenital area are among the high-risk areas for ulceration, dysfunction, or disfigurement and thus require treatment [6]. Although the majority of haemangiomas are benign and disappear on their own, about 10% may result in aesthetic and life-threatening complications.

Ineffective hemangiomas can now be treated pharmacologically with beta-blockers, bleomycin, interferon-alpha, vincristine, steroids, and imiquimod [7, 8]. These treatments all have different side effects and only modest therapeutic benefits. Sir James W. Black made the discovery of propranolol as a beta-adrenergic receptor antagonist. The impact of the beta-blocker propranolol on complex infantile haemangiomas has been discovered to be significant in medicine. Leaute-Labreze *et al.* [9] treated a child with corticosteroids for a nasal capillary haemangioma, and this led to the first observation. A beta-blocker called propranolol was used to treat the child's obstructive hypertrophic cardiomyopathy, which was a regrettable side effect of the corticosteroid therapy. The haemangioma softened, changed color, and did not regrow after the corticosteroids were stopped on the day that treatment began. A large haemangioma with intraconal and extraconal orbital involvement, as well as an intracervical mass causing compression and esophageal and tracheal deviation, were present in the second infant, who needed propranolol due to increased cardiac output. After a week, the mass had significantly diminished and the child could now open his eyes. When the corticosteroids were stopped, there was no regrowth of the hemangioma. Following these two occurrences, propranolol was administered to nine additional infants with severe or disfiguring infantile capillary haemangiomas, and Leaute-Labreze *et al.* [9] noted the same startling clinical responses they had observed in the first two patients.

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Since the accidental observation by Leaute-Labreze *et al.* [9], the use of propranolol for hemangioma treatment has now become a subject of extensive investigation. When treating infants with cardiac and renal conditions, propranolol - a non-selective -adrenergic antagonist with equal affinity for both beta-1 and beta-2 receptors - is often used. Due to its lipophilic properties, it also exhibits certain membrane stabilizing characteristics. The advantages of propranolol are its rapid onset of action resulting in clinical improvement, less serious side effects than systemic steroids and is inexpensive. It can also be used for hemangiomas even beyond the proliferative phase.

Materials and Methods

This prospective study was conducted in Department of Pediatrics, Navodaya Medical College Hospital and Research Centre, Mantralayam Road, Raichur, Karnataka, India over a period April 2021 to March 2022. All children with hemangiomas attending in hospital outpatient department during the study period.

Inclusion criteria

- Multiple lesions [Lesions greater than one are considered as multiple lesions].
- Single or multiple lesions with complications-Cosmetic / Functional risks (Ulceration, bleeding, Feeding problems, Vision related – Proptosis, Ptosis, Upper airway obstruction).
- Single or multiple lesions with rapid proliferation – defined as doubling in size over one to two weeks.
- Hemangiomas on drug therapies other than propranolol with no improvement.

Exclusion criteria

- History of allergy or hypersensitivity to beta-blockers
- Children with risk factors for beta blocker usage
- Cardiac - Congenital heart disease Sinus Bradycardia
- Congestive heart failure Atrioventricular block
- Respiratory
- Past history of wheeze
- Family history of Bronchial Asthma
- Hemangiomas associated with visceral lesion
- Hemangiomas with syndromic associations

Ethics Committee Approval

Approval was obtained from the Institutional Research Ethics committee (CTMRF-CHILDS Trust Medical Research foundation) prior to conducting this study.

Results

Propranolol therapy

Table 1: Duration of propranolol therapy

Item	Finding
Mean age at start of treatment (months)	5.27 ± 3.09 (Range-1-12m)
Mean duration of treatment (months)	9.61± 2.82 (Range 5-20m)

Data are presented as mean values ± SDs (ranges).

Mean age at starting of Propranolol treatment was 5.27months with a range of 1 to 12 months. Mean duration of treatment was 9.61months with a range of 5 to 20 months.

Table 2: Propranolol dose administered was 2- 3mg/kg/day.

	Superficial Hemangiomas	Deep Hemangiomas
Mean duration of therapy in months	8.96±1.71	8.8±2.10

Data are presented as mean values ± SDs

The mean duration of propranolol therapy for superficial and deep hemangiomas was 8.96 months and 8.8 months respectively.

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Table 3: Mean duration of propranolol therapy in different hemangiomas regions

	Head Region	Trunk Region	Extremities
Mean duration of therapy in months	9.72±3.12	8.6±1.73	10.5±1.91

Data are presented as mean values ± SDs

For the hemangiomas in the head region, the mean duration of propranolol therapy was 9.72months and for the hemangiomas in the trunk and extremities it was 8.6 and 10.5 months respectively.

Outcome of hemangiomas on propranolol treatment

Regression

Regression in size, which was calculated as a percentage and divided into different responses based on the percentage of regression on a scale from 0% to 100%, was used to objectively measure response to treatment. A regression in size of 76-100% was taken as excellent response (E), 51-75% as good response (G), 26 to 50% as fair response (F) and 25% or less as poor response (P).

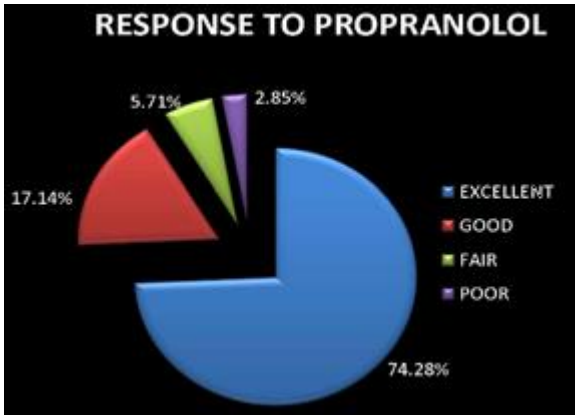

Fig 1: Response to propranolol

74.28% (26) of hemangiomas showed excellent response, 17.14 % (6) showed Good response, 5.71% (2) showed fair response and 2.85 % (1) showed poor response to propranolol therapy.

Table 4: Size if hemangiomas before and after propranolol therapy

S. No	Initial size of hemangioma in centimeters	Size of hemangioma in centimeters after propranolol therapy	% Regression	Response
1	1.5 x 1	0.5 x 0.5	66.67	G
2	3.8 x 1.3	0.5 x 0.5	86.84	E
3	1.5 x 1.3	0.7 x 0.5	53.34	G
4	1.8 x 3 x 1.6	0	100	E
5	7 x 4	1 x 0.5	85.7	E
6	5 x 3	0.5 x 0.5	90	E
7	2 x 1	0.5 x 0.5	75	G
8	3 x 2	0.5 x 0.5	83.33	E
9	3 x 3	0.5 x 0.5	83.33	E
10	5 x 6	1 x 0.5	83.33	E
11	15 x 5	3 x 2	80	E
12	2 x 2	0	100	E
13	2 x 2	0	100	E
14	2 x 2	0	100	E
15	3 x 2	1 x 0.5	83.33	E
16	7 x 4	3 x 1.5	57.14	G
17	15 x 8	3 x 2	80	E
18	5 x 4	0	100	E
19	7 x 5	1 x 0.5	85.7	E
20	3 x 2	0.5 x 0.5	83.33	E
21	4 x 4	0	100	E
22	2 x 2	0	100	E
23	1 x 1	0	100	E
24	3 x 2	0	100	E
25	5 x 5	4 x 4	20	P

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26	2 x 2	0	100	E
27	5 x 5	1 x 0.5	80	E
28	3 x 3	0.5 x 0.5	83.33	E
29	3 x 2	0.5 x 0.5	83.33	E
30	3 x 2	0	100	E
31	5 x 4	3 x 3	40	F
32	2.5 x 1.5	0	100	E
33	3.5 x 4.2	1.8 x 2	57.14	G
34	6 x 5	3 x 3	50	F
35	3.5 x 2	1 x 0.5	71.4	G

Degree of freedom-35 $p<0.001$

The size of hemangiomas at the start and at the end of the treatment was compared. Paired t-test (Student's t-test) was applied and p value was statistically significant ($p \leq 0.001$). The regression in size of hemangiomas with propranolol therapy was statistically significant.

Table 5: Regression percentage vs. Type of hemangioma

Type of Hemangioma	Number of Hemangiomas	Mean Regression in size	Standard Deviation	Minimum Regression in size	Maximum Regression in size
Compound	4	72.618	23.207	50.00	100.00
Deep	10	86.587	10.777	66.67	100.00
Superficial	21	81.233	22.223	20.00	100.00

F=0.731 p=0.489

ANOVA test was applied for comparing the regression of hemangiomas in size with reference to type of hemangiomas. The regression in size of hemangiomas with propranolol therapy with reference to type of hemangiomas was not statistically significant.

Table 6: Regression percentage vs. Site of Hemangioma

Site of Hemangioma	Number of Hemangiomas	Mean Regression in size	Standard Deviation	Minimum Regression in size	Maximum Regression in size
Head	21	79.953	23.294	20.000	100.00
Trunk	10	87.323	7.701	75.000	100.00
Extremities	4	77.500	20.616	50.000	100.00

F=0.569, p=0.571

With reference to the site of hemangioma, the regression in size with propranolol therapy was not statistically significant.

Residual deformity

Out of 35 hemangiomas, 4 (11.4%) hemangiomas had residual scarring after regression.

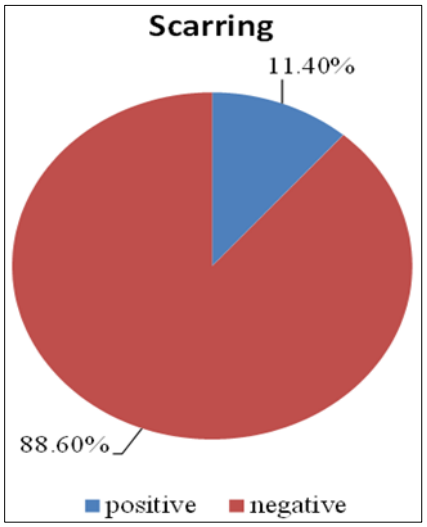

Fig 2: Relapse of hemangioma after propranolol therapy

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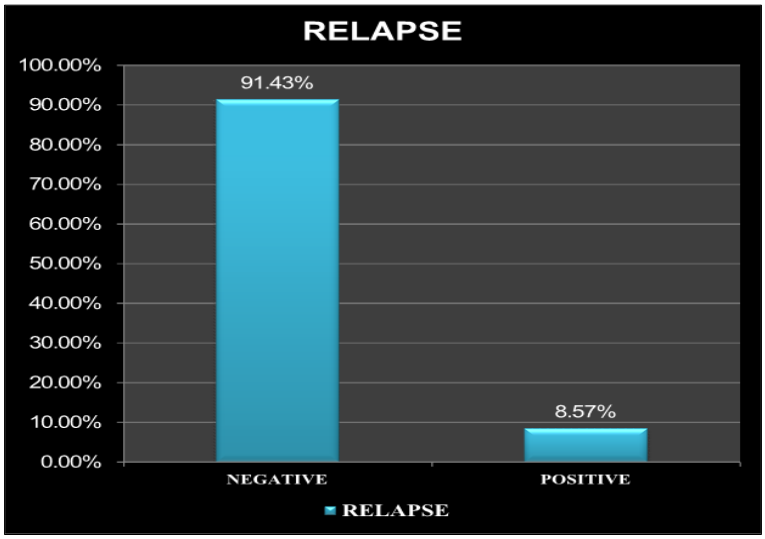

Fig 3: Relapse

Out of 35 hemangiomas, 3(8.57%) had relapse in the form of rebound growth after regression, out of them 2 had relapse 6months after stopping treatment and one had relapse 3 months after stopping treatment.

Parents feedback on lesions

Parents of 27 children (90%) felt there was improvement both in colour and size of hemangioma with the propranolol therapy. For the remaining 3 chidren, parents have not felt improvement either in size or colour of hemangioma.

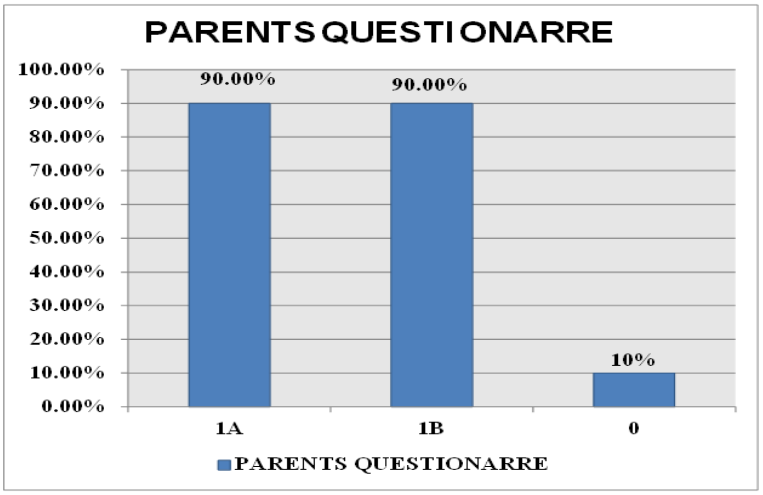

Fig 4: Parents Questionarre

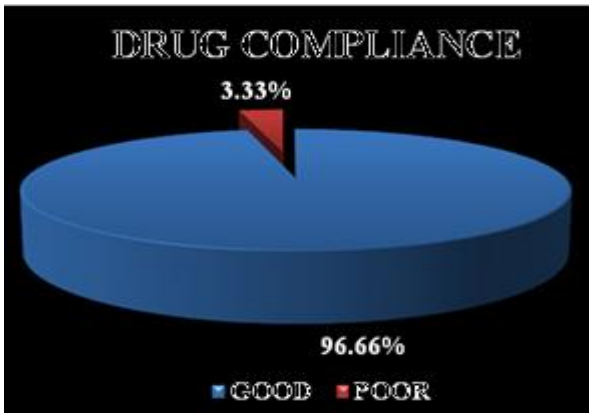

Fig 5: Drug compliance

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Out of 30 children, one (3.33%) had poor drug compliance.

Discussion

The mean duration of propranolol therapy for superficial and deep hemangiomas was 8.96 months and 8.8 months respectively. For the hemangiomas in the head region, the mean duration of propranolol therapy was 9.72months and for the hemangiomas in the trunk and extremities it was 8.6 and 10.5 months respectively.

In our study we have used a propranolol dose ranging from 2- 3mg/kg/day in 3 divided doses. Out of 35 hemangiomas, 26 (74.28%) showed excellent response with complete resolution of 12 hemangiomas. 6 hemangiomas (17.14%) showed good response and 2(5.71%) showed fair response. The regression in size of hemangiomas with propranolol therapy was statistically significant (p value <0.001).

Only one hemangioma showed poor response. This infant presented at a late stage (at 12months of age). The poor response in this child may be because the hemangioma was in the stationary (Post proliferative) phase when he was started on treatment with propranolol.

Further evidence for this theory came from previously published research showing that propranolol is most effective during the proliferative phase of hemangiomas [10]. A dose of 1.5 to 3 mg/kg per day of propranolol was used to treat children aged 7 months to 10 years for 1 to 8 months in a multicenter retrospective study by Zvulunov *et al*. [11], and the regression of hemangiomas was documented.

There was no statistically significant difference in response to propranolol therapy with reference to the type of hemangioma (superficial, deep and compound) and with reference to the site of hemangiomas (head versus trunk and extremities). Similar observations have been reported earlier by Haded *et al*. [12], in his study.

For the treatment of infantile hemangiomas, various propranolol regimens were reported. In their study, Qin *et al*. [13] found that 67% of patients receiving propranolol at doses of 1.5–2.0 mg/kg/day responded "good to excellently." In a study by Zaher *et al*. [14], propranolol at a dose of 2 mg/kg/day resulted in a good to excellent response in 80% of the infants. In contrast, Holmes *et al*. [15] used a high dose of propranolol (3 mg/kg/day) in their study of 31 children, and 87% of the patients experienced significant regression, while 13% showed no signs of regression over the course of treatment.

Haded *et al*., [12] in his study with a propranolol dose of 2- 3mg/kg/day and a mean duration of therapy of 5 months reported complete resolution of the lesion in 66.7% (16), good response with a more than 50% reduction in the size of the lesions in 16.7% (4), and fair response with less than 50% reduction in the size of lesions in 12.5% (3).

Out of 35 hemangiomas, 3 hemangiomas (8.57%) showed relapse in the form of rebound growth. Out of them, two had relapsed 6months after stopping treatment and one after 3 months. These children initially had a good to excellent response to therapy. They received relatively shorter courses of treatment with a range of 5months-6.26 months and a propranolol dose ranging 2.2-2.3mg/kg/day and stopped while they were still younger than 9 months. Rebound growth in these children may be explained by the fact that infantile hemangiomas continue to proliferate until they are 7 months old. By the age of 8 months, this phase gradually ends as the ratio of pro-apoptotic to pro-angiogenic factors changes [15]. Propranolol treatment should be continued until an average age of 14.2 months, according to Itinteang *et al*.'s recommendation [16].

Haded *et al*., [12] in his study with 24 children with a mean duration of propranolol therapy of 5 months reported relapse in the form of rebound growth in 4(16.66%) children 2weeks after cessation of therapy. In contrast, Sabbagh *et al*., [17] with 15 children with a mean duration of therapy of 4 months has not reported any relapse.

All children tolerated propranolol therapy well. No one had required interruption or withdrawl of therapy due to side effects. Similarly Chung *et al*., [18] and Xiao *et al*., [19] in their studies with 8children and 64 children respectively, with a propranolol dose of 2mg/kg/day has not reported any side effects. This substantiates the recommendation that routine cardiac evaluation before propranolol therapy is not needed and reinforces the need for careful clinical evaluation before propranolol therapy [20].

In contrast Buckmiller *et al*., [21] with 41 children, has reported minor side effects including increased somnolence (27.3), gastro esophageal reflux (9.1) and allergic rash (4.5%).

In our study, parents of 27 infants (90%) reported improvement both in colour and size as per the questionnaire given to them. In a study by Buckmiller *et al*. [21] overall opinion of parents for propranolol treatment was ‘‘happy with the response, would recommend’’ in 20 of 22 patients (90.9%) and ‘‘neutral’’ in 2 of 22 patients (9.1%).

Conclusion

There was no statistically significant difference in response to propranolol therapy with reference to type and site of hemangiomas. 90% parents have noticed improvement both in colour and size of hemangiomas with propranolol therapy. Rebound growth was noted in 8.57% and 11.4% of

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hemangiomas had residual scarring after regression. All children tolerated propranolol well without significant side effects. No one had required interruption or withdrawal of propranolol therapy for side effects.

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Conflict of interest
None

References

1. Kilcline C, Frieden IJ. Infantile Hemangiomas: How Common Are They? A Systematic Review of the Medical Literature. Pediatr Dermatol. 2008;25:168-173.
2. Frieden IJ, Haggstrom AN, Drolet BA, Mancini AJ, Friedlander SF, Boon L. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. Pediatr Dermatol. 2005;22(5):383–406.
3. Li J, Chen X, Zhao S. Demographic and clinical characteristics and risk factors for infantile hemangioma: A Chinese case-control study. Arch Dermatol. 2011;147(9):1049-1056.
4. Haggstrom AN, Drolet BA, Baselga E. Hemangioma Investigator Group. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr. 2007;150(3):291–294.
5. Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. Arch Dermatol. 1960;82:667–80.
6. Mendiratta V, Jabeen M. Infantile hemangioma: an update. Indian J Dermatol Venerol Leprol. 2010;76:469-475.
7. Mabeta P, Pepper MS. Hemangiomas – current therapeutic strategies. Int J Dev Biol. 2011;55:431-437.
8. Itinteang T, Withers AH, Leadbitter P, Day DJ, Tan ST. Pharmacologic therapies for infantile hemangioma: is there a rational basis? Plast Reconstr Surg. 2011;128:499-507.
9. Leaute-Labreze C, de la Roque ED, Hubiche T. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649-51.
10. McGee P, Miller S, Black C, Hoey S. Propranolol for infantile haemangioma: A review of current dosing regime in a regional paediatric hospital. Ulster Med J. 2013;82:16-20.
11. Zvulunov A, McCuaig C, Frieden IJ. Oral propranolol therapy for infantile hemangiomas beyond the proliferative phase: a multicenter retrospective study. Pediatr Dermatol. 2011;28 (2):94–8.
12. Haded HMA, Fathy A, Khalil AA. Oral Propranolol: A Corner Stone in the therapeutic strategy of Infantile Haemangiomas. Int J Cardiovasc. 2015;4:2.
13. Qin ZP, Liu XJ, Li KL. Treatment of infantile hemangiomas with low dose propranolol: evaluation of short term efficacy and safety. Zhonghua Yi Xue Za Zhi. 2009;89:3230–3234.
14. Zaher H, Rasheed H, Hegazy RA, Hegazy RA, Abdelhalim DM. Oral propranolol: an effective, safe treatment for infantile hemangiomas. Eur J Dermatol. 2011;21:558-563.
15. Holmes WJ, Mishra A, Gorst C, Liew SH. Propranolol as first line treatment for rapidly proliferating infantile haemangiomas. J Plast Reconstr Aesthet Surg. 2011;64:445-451.
16. Itinteang T, Withers AH, Davis PF, Tan ST. Biology of infantile hemangioma. Front Surg. 2014;1(38):38.
17. El-Sabbagh AH. Oral Propranolol: A Useful Treatment for Infantile Hemangioma. J. Biomedical Science and Engineering. 2015;8:441-450.
18. Chung SH, Park DH, Jung HL, Shim JW, Kim DS, Shim JY, *et al*. Successful and safe treatment of hemangioma with oral propranolol in a single institution. Korean J Pediatr. 2012;55(5):164-170.
19. Xiao Q, Li Q, Zhang B, Yu W. Propranolol therapy of infantile hemangiomas: efficacy, adverse effects and recurrence. Pediatr Surg Int. 2013;29:575-581.
20. Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Diagnosis and Management of Infantile Hemangioma. Pediatrics. 2015;136(4):1060-104.
21. Buckmiller LM, Munson PD, Dyamenahalli U. Propranolol for infantile hemangiomas: Early experience at a tertiary vascular anomalies center. Laryngoscope. 2010;120:676-81.