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ROLE AND SAFETY OF ORAL PROPRANOLOL IN INFANTILE HAEMANGIOMAS

Dr Dipesh Goel[1*], Dr Gaurav Singal[2], Dr Prateek Sharda[3]

[1*]Associate Professor, Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala.
[2]Associate Professor, Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala.
[3]Associate Professor, Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala.

***Corresponding Author:** DR Dipesh Goel
*Associate Professor, Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. Email: dipeshsurindergoel@yahoo.com

Abstract

Background and objectives Infantile haemangiomas (IHs) are the most common benign vascular tumors seen in neonatal period. Some presents with life-threatening complications, functional impairment, ulceration and disfigurement requiring intervention. Oral propranolol is the first line treatment for the IHs in these high-risk group. It reduces the size of lesion by inducing vasoconstriction, decreasing vascular endothelial growth factor (VEGF), induction of endothelial cell apoptosis, inhibition of nitric oxide production, and suppression of the renin-angiotensin system. Propranolol is contraindicated in children with bronchial asthma, hypoglycaemia, heart blocks and hypersensitivity to propranolol. Some non-serious side effects are sleep disturbances, irritability, diarrhoea and lethargy, thus requiring dose titration. So, to determine the effectiveness and safety of oral propranolol therapy in IHs a study is proposed.

Methodology A retrospective study was conducted from May 2022 to October 2023. Inclusion and exclusion criteria were applied, n = 21. Oral propranolol was stared at the dose of 1mg/kg/day after obtaining baseline heart rate (HR), blood pressure (BP), ECG and 2DECHO on OPD basis. The dose was then increased gradually (0.5mg/kg/day in each visit) to maximum of 3 mg/kg/day given in divided doses. Serial clinical examination (HR & BP), ECG and 2DECHO was done prior to increase the dose. These were also repeated in case development of adverse effects to propranolol therapy. Intolerable adverse effects were treated by dose titration. Oral propranolol therapy was continued for complete 1 year after initiating it.

Results IHs were commonly seen in females (71%) vs male (29%). The most common site of IHs was head, neck and face region (HNF – 57.1%). This was followed by trunk (28.6%) and limbs (14.3%). There was decrease in tenseness and brightness of the lesion in all children. There was decrease in longest length of the IHs lesion by 72.95% after 12 months of oral propranolol therapy ($P < 0.0001$) at the dose of 2.6mg/kg/day. Dizziness was the most common side effect seen which can be managed by dose titration.

Conclusions Oral propranolol therapy is the first line, safe and effective treatment in Infantile haemangiomas. There are no major side effects of the therapy and it can be given safely in OPD settings.

Key words Infantile haemangiomas (IHs), Propranolol

Introduction

Infantile haemangiomas (IHs) are the most common benign vascular tumors seen in neonatal period. In India the prevalence is 1 to 2.8 neonates per 1000 live births[1]. They are more commonly seen in female[2]. They are usually not seen at birth but appear in first two weeks of life. They are seen as telangiectatic red spot or mimics a bruise. They also develop in visceral organs around 4 months of age[3]. There is rapid growth of haemangiomas during first 6 months of infancy (proliferative phase). Then they grow slowly till 1st year of life. This is then followed by regression in the size of haemangiomas (involuting phase). They completely regress by 5 to 10 years of life and require no treatment. There are some haemangiomas which can be labelled as high risk. They are the ones with life-threatening complications, functional impairment, ulceration and disfigurement. Life threatening complications can be seen in subglottic haemangiomas as they lead to obstruct the airway. Similar threat to life is seen in large haemangiomas leading to high output cardiac failure. IHs on lips and oral cavity leads to feeding difficulties. Periocular haemangiomas lead to visual difficulties leading to astigmatism. Some of the haemangiomas complicate by ulceration, bleeding and infection. While others can lead to permanent disfigurement. Therefore, these high risk haemangiomas need early intervention. Most of the time the diagnosis is clinical. Before any intervention a doppler USG with doppler is done. It will tell us about the size, extensions of the lesion, high flow vascularity and absence of arteriovenous shunting of the blood.

Oral propranolol is the first line treatment for the IHs in high risk group[4]. The recommended dose of propranolol for IHs is 2–3 mg/kg/day in divided dose given BD. This is then continued till 1 year of age. The mechanism of action of propranolol in IHs is unclear. The proposed mechanisms are vasoconstriction, angiogenesis inhibition by decreased VEGF, induction of endothelial cell apoptosis, inhibition of nitric oxide production, and suppression of the renin-angiotensin system[5]. It is contraindicated in neonates, infants with bronchial asthma, hypoglycaemia, heart blocks and hypersensitivity to propranolol. Some non-serious side effects are sleep disturbances, irritability, diarrhoea and lethargy, thus requiring dose titration. To prevent the adverse effects the oral propranolol is started at a dose of 1 mg/kg/day. It is then gradually increased to between 2-3 mg/kg/day in divided doses under monitoring. Base line clinical examination, ECG and 2DECHO is done. This is then repeated serially in outpatient visits to know any change from baseline status and the dose is titrated accordingly.

Aims

This study aims to determine the effectiveness of oral propranolol therapy in IHs. It can be evaluated by assessing the decrease in the size of IHs in response to propranolol therapy. To determine the adverse effects with oral propranolol therapy.

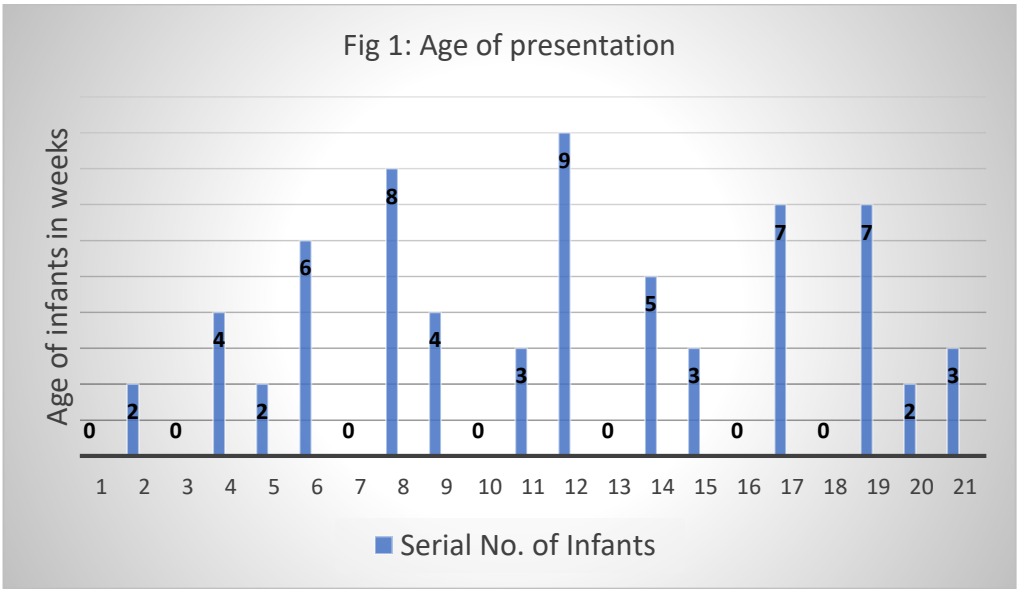
Methodology

A retrospective study was conducted from May 2022 to October 2023 at MMIMSR, Mullana, Ambala. Infants with IHs causing functional difficulties, ulceration, bleeding, infection and those causing disfigurement were included. Infants with haemangiomas causing airway compromise and high output failure were excluded, as they require multidisciplinary team approach with multimodality treatment. Infants with bronchial asthma, hypoglycaemia, heart blocks and intolerable adverse effects refractory to dose titration of propranolol were also excluded. Oral propranolol was stared at the dose of 1mg/kg/day after obtaining baseline heart rate (HR), blood pressure (BP), ECG and 2DECHO on OPD basis. The dose was then increased gradually (0.5mg/kg/day in each visit) to maximum of 3

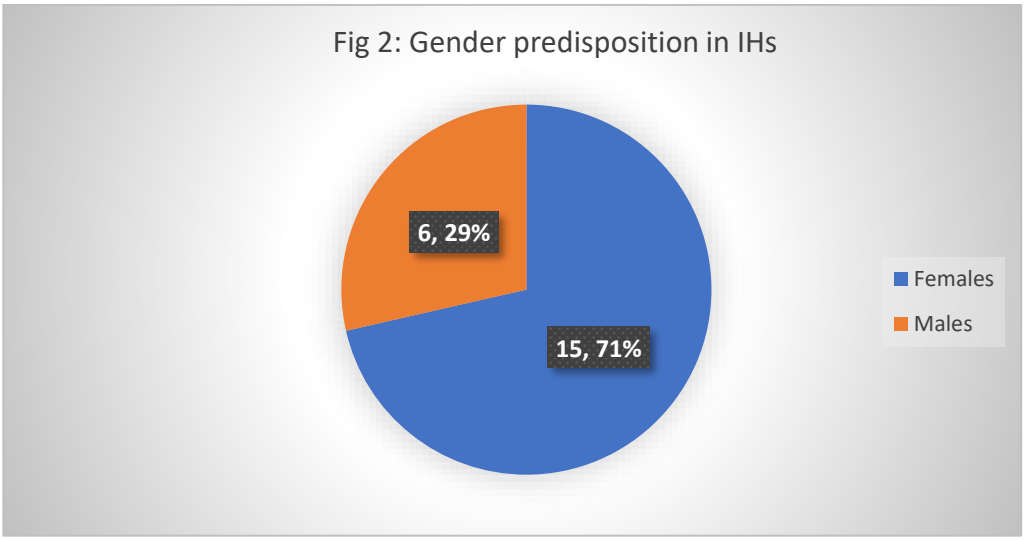
mg/kg/day given in divided doses[6]. Serial clinical examination (HR & BP), ECG and 2DECHO was done prior to increase the dose. These were also repeated in case development of adverse effects to propranolol therapy. Intolerable adverse effects were treated by dose titration. Oral propranolol therapy was continued for complete 1 year after initiating it. Records of age, sex, location of lesion, longest dimension, ECG, 2DECHO, dosage of propranolol and adverse effects profile were noted. Serial photographs at the first visit, every follow up visit (3,6,9,12 months) were taken. Response to treatment was evaluated with repeated clinical examinations. IHs becoming less bright or pale, reduction in tenseness on palpation and decrease in longest dimension was considered as good response to propranolol therapy. The dosage requirement and adverse effects of the oral propranolol therapy was also noted. Results were tabulated, statistically analysed using paired t test and discussed.

Results

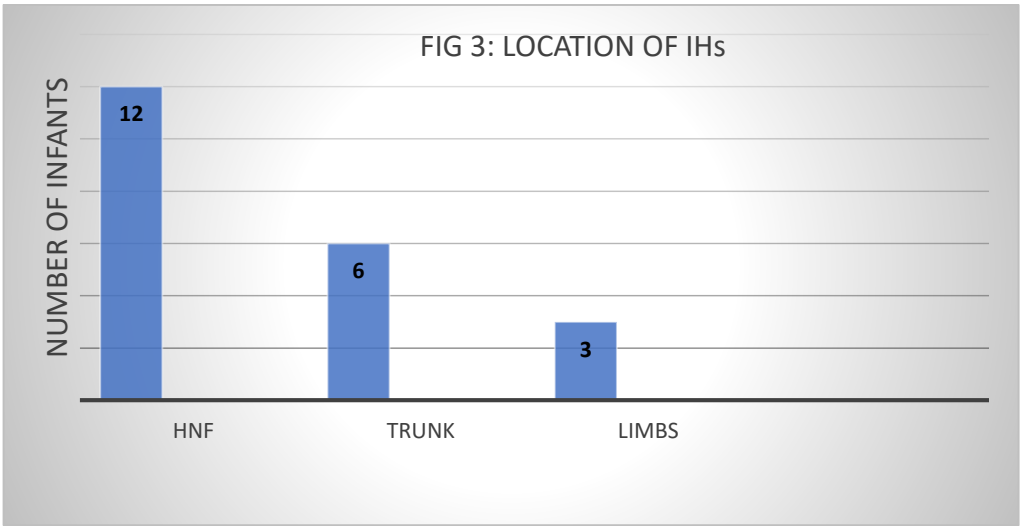
A case series of 29 children with IHs were studied. Eight children were not considered in sample size after applying the exclusion criteria (n = 21). 7 (33.33%) children presented with IHs at birth. Rest 14 (66.66%) children presented in first few weeks of life as shown in fig 1. The mean age of appearance of IHs was 3 weeks.



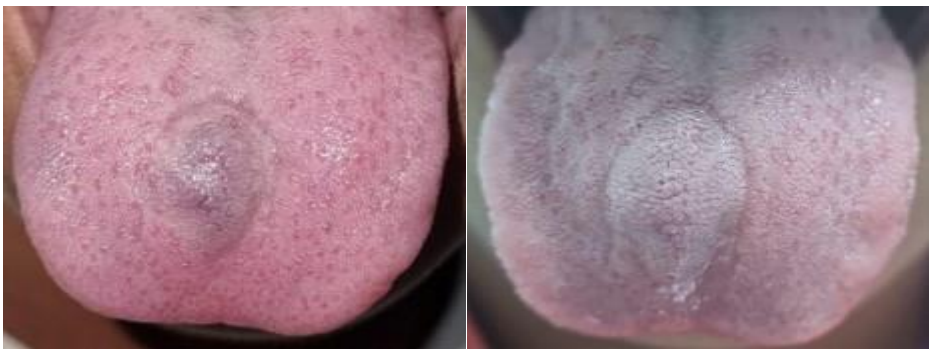
They presented with a cutaneous telangiectatic spots mimicking a bruise. IHs were more commonly seen in females in ratio of 2.1:1. Fifteen children were female and six were male as shown in fig 2.



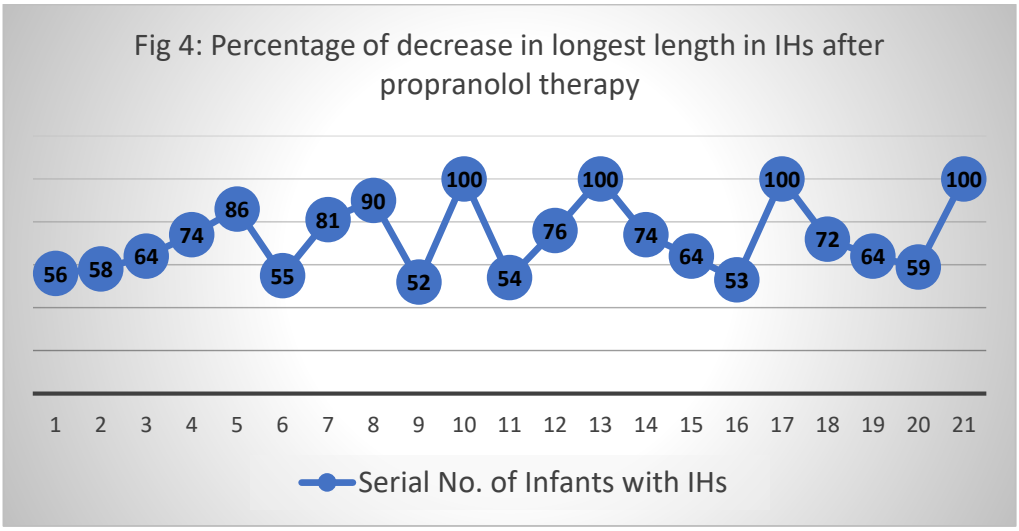
Twelve children developed IHs in HNF (head, neck & Face). Six had the lesion on trunk and three had on limbs as shown in fig 3.



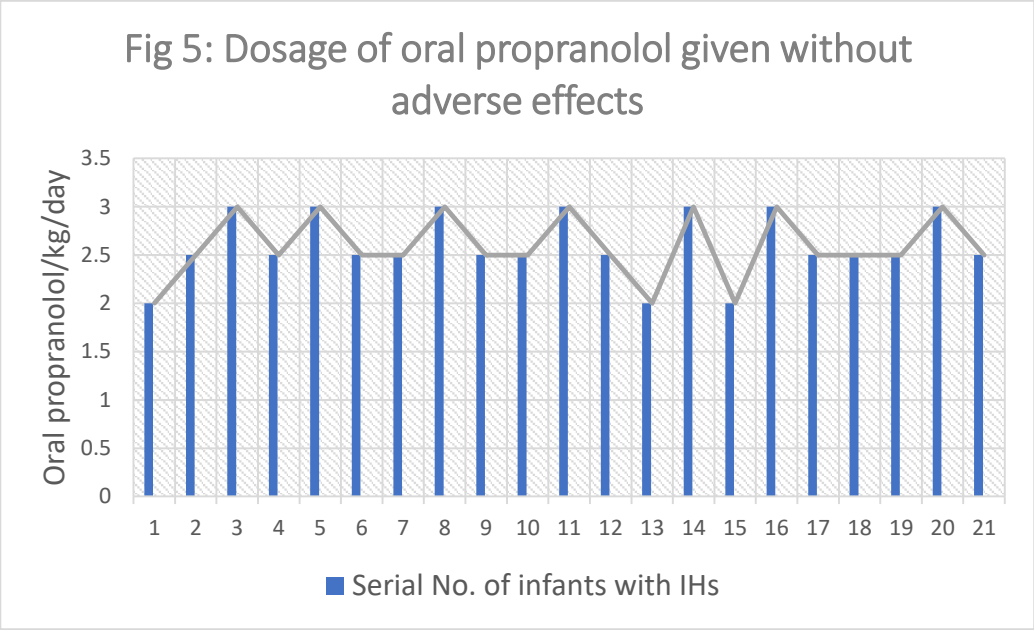
In all the 21 children there was decrease in the tenseness at a mean duration of 4.5 weeks after initiation of propranolol therapy. All the children also showed colour change of the lesion to less bright at the mean duration of 15 weeks of therapy as shown in picture1 & 2. There is decrease in longest length of the IHs lesion by 72.95% after 12 months of oral propranolol therapy (P< 0.0001).



Picture: 1 shows haemangioma of tongue before initiation of the propranolol therapy.
Picture 2 shows decrease in tenseness and change of colour after initiation of propranolol therapyin the same child.



The mean dosage of oral propranolol at which there is 72.95% reduction in longest length of the IHs was 2.6 mg/kg/day without any intolerable side effect as shown in fig 5. Two children developed dizziness, which responded to dose titration.



Discussion

Infantile Haemangiomas (IHs) were the most common benign vascular tumours seen in infants visiting our hospital. In our study 7 (33.33%) children presented with IHs at birth. Rest 14 (66.66%) children presented in first few weeks of life. The mean age of appearance of IHs was 3 weeks. Similar findings were seen in literature. It is usually diagnosed between 1st to 4th week of life[3]. They may be noticed later in life. It occurs when proliferative phase was seen beyond three years[7]. In our study IHs were more commonly seen in females in ratio of 2.1:1. Fifteen children were female and six were male. Female preponderance in IHs was also observed in literature[8]. In our study twelve children developed IHs in HNF (head, neck & Face). Six had the lesion on trunk and three had on limbs. Head and neck region was the commonest site of the IHs followed by trunk and extremities[3,9]. In all the children there was decrease in the tenseness at a mean duration of 4.5 weeks after initiation of propranolol therapy. All the children also showed colour change of the lesion to less bright at the mean duration of 15 weeks of therapy. In four of the children with IHs there was complete resolution of the lesion. There was decrease in longest length of the IHs lesion by 72.95% after 12 months of oral propranolol therapy. Similar response to oral propranolol therapy in IHs was observed in literature. There was reduction in size of the lesion by 30% to 70%[6,10]. In our study the mean dosage of oral propranolol at which there is 72.95% reduction in longest length of the IHs was 2.6 mg/kg/day without any intolerable side effect. Two children developed dizziness in which the oral dose was titrated. In literature regimen of oral propranolol in a dose of 1-3 mg/kg/day have been found to give satisfactory result in IHs[6,11].

Conclusions Oral propranolol therapy is very effective in terms of decreasing the size of IHs. After initiation of therapy, there is decrease in tenseness of the lesion. This is followed by change in colour. The lesions become less bright. Then it is followed by decrease in the longest dimension of the IHs. Some of the IHs completely resolve, while others can be resected surgically with minimal scarring. The therapy in a dose between 2.5 to 3 mg/kg/day is well tolerated under close observation. Regular follow up is required to determine adverse effects of propranolol therapy, which can be treated with dose titration. There are no major adverse effects of the therapy. To conclude oral propranolol when given in infantile haemangiomas under close supervision is safe and effective.

Conflict of interest NIL

References

1. Abraham A, Job AM, Roga G. Approach to Infantile Hemangiomas. Indian J Dermatol. 2016 Mar-Apr;61(2):181-6. doi: 10.4103/0019-5154.177755. PMID: 27057018; PMCID: PMC 4817443.
2. Qian Lin, Beichen Cai, Xiuying Shan, Xuejun Ni, Xuanfeng Chen, Ruonan Ke, Biao Wang, Global research trends of infantile hemangioma: A bibliometric and visualization analysis from 2000 to 2022, Heliyon, Volume 9, Issue 11, 2023, e21300.
3. Jung HL. Update on infantile hemangioma. Clin Exp Pediatr. 2021 Nov;64(11):559-572. doi: 10.3345/cep.2020.02061. Epub 2021 May 26. PMID: 34044479; PMCID: PMC8566803.
4. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical practice guideline for the management of infantile hemangiomas. Pediatrics. 2019;143:e20183475.
5. Chen ZY, Wang QN, Zhu YH, Zhou LY, Xu T, He ZY, et al. Progress in the treatment of infantile hemangioma. Ann Transl Med. 2019;7:692.
6. Aletaha M, Salour H, Bagheri A, Raffati N, Amouhashemi N. Oral propranolol for treatment of pediatric capillary hemangiomas. J Ophthalmic Vis Res. 2012 Apr;7(2):130-3. PMID: 23275821; PMCID: PMC3520472.
7. Kathleen F. O'Brien, Sonal D. Shah, Elena Pope, Roderic J. Phillips, Francine Blei, Eulalia Baselga, Maria C. Garzon, Catherine McCuaig, Anita N. Haggstrom, Peter H. Hoeger, James R. Treat, Marissa J. Perman, Jane S. Bellet, Xavier Cubiró, Jeffrey Poole, Ilona J. Frieden, Late growth of infantile hemangiomas in children >3 years of age: A retrospective study, Journal of the American Academy of Dermatology, Volume 80, Issue 2, 2019, Pages 493-499, //doi.org/10.1016/j.jaad.2018.07.061.
8. F.J. Melgosa Ramos, T. Díaz-Corpas, S. Santos-Alarcón, M. Galarreta Pascual, A. Aguado Vázquez, A. Mateu Puchades, Congenital and Infantile Hemangiomas: Epidemiological, Clinical, and Treatment Characteristics Based on 3 Years' Experience at a Tertiary Care Hospital – A Retrospective Case Comparison and Review of the Literature, Actas Dermo-Sifiliográficas, Volume 114, Issue 7, 2023, Pages T631-T635, ISSN 0001-7310, //doi.org/10.1016/j.ad.2023.01.017.
9. Sethuraman G, Yenamandra VK, Gupta V. Management of infantile hemangiomas: current trends. J Cutan Aesthet Surg. 2014 Apr;7(2):75-85. doi: 10.4103/0974-2077.138324. PMID: 25136206; PMCID: PMC4134656.
10. Tan X, Guo S, Wang C. Propranolol in the Treatment of Infantile Hemangiomas. Clin Cosmet Investig Dermatol. 2021;14:1155-1163 //doi.org/10.2147/CCID.S332625.
11. Prasad A, Sinha AK, Kumar B, Prasad A, Kumari M. Individualized dosing of oral propranolol for treatment of infantile hemangioma: a prospective study. Pan Afr Med J. 2019 Apr 8;32:155. doi: 10.11604/pamj.2019.32.155.16760. PMID: 31303926; PMCID: PMC6607273.