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Original Research Article

Role of propranolol in the management of infantile hemangioma

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ABSTRACT

Background: Infantile hemangiomas are the most common benign soft tissue tumor of infancy and childhood occurring 4-10% of all infants. It is more frequent in premature children (23% of infants <1200g) and females (3:1 to 5:1). For many hemangiomas treatment is not required, however hemangioma in some locations need treatment to prevent complication. The Present study was done with an Aim to assess the efficacy and safety of oral Propranolol in management of infantile heamangioma in our set-up.
Methods: This study was conducted from May 2016 to Nov 2017 at Department of Surgery and Pediatrics, M.L.B. Medical College, Jhansi after obtaining Ethical permission. Patients having confirmed were recruited & admitted for initiation of Oral Propranolol therapy for 5 days under the observation of Paediatrician. Oral Propranolol treatment was continued till the age of 11/2 years. A clinical assessment was made at each visit to the Outpatients Clinic every four weeks.
Results: The incidences of infantile hemangioma were more in age group (0-7 months) i.e 55% (22 patients) followed by age group of (8-15 days) i.e. 30% (12 patients). As age advances presentation gradually decreases as after 30 days incidence is only 5%. Infantile hemangioma were more common in females' patients (55% patients) & mostly 90% (36 patients) present as single lesion and only 10% (4 patients) present as multiple lesions. Most of hemangiomas presented as reddish in color 80% (32 patients) which reflected lesions are mostly superficial & only 10% were brownish red and 10% skin color indicated incidence of deeper penetration.
Conclusion: Authors found that drug (Propranolol) to be effective even at low dose of 1mg/kg/day. In our study group it was effective and safe in almost all patients.

Keywords: Age, Infantile hemangioma, Lesion, Patients, Propranolol, Treatment

INTRODUCTION

Infantile hemangioma (IH) (sometimes called a strawberry birthmark) is a benign vascular, soft-tissue tumour that affects 4% to 10% of infants.[1] Infantile hemangioma can be grouped into focal, segmental and indeterminate or depending on the depth of the lesion from the skin surface as superficial, deep and mixed.

Most infantile hemangiomas resolve spontaneously, without treatment, but some may warrant medical or surgical treatment because of interference with function, significant disfigurement or, in rare cases, life-threatening physiologic compromise.[2-3]

The treatment of Infantile Hemangioma (IH), the most common childhood tumor with an incidence of 4-5%, has

undergone a revolution since the observation in 2008 of dramatic regression of IH with oral propranolol, a nonselective β-adrenergic receptor–blocking agent. Although most IHs resolve naturally without treatment, approximately 10% to 15% cause complications requiring intervention.[4]

Recently, there has been an interest in Propranolol and other beta-blockers in the treatment of IH. Propranolol may be more effective and safer than previously established therapies and may be an alternative when more widely accepted treatments for IH have failed. Initial studies suggest that it may also be used as a first-line therapy.

The mechanism of actions of propranolol may include vasoconstriction, decreased expression of VEGF (Vascular endothelial growth factor) or bFGF (Basal fibroblast growth factor) genes down regulation of the RAF-mitogen-activated protein kinase pathway or triggering of apoptosis of endothelial cells.

Other selection criteria may include lesion location that is inaccessible to surgery, lesions with a deep component, severe ulceration and/or cosmetic disfigurement, obstruction of airway or visual axis, and the presence of contraindications to other medical therapies. Parental apprehension remains an important indication for treatment in cutaneous IH, irrespective of the possibility of spontaneous involution.

The present study was done to assess the efficacy and safety of oral propranolol in management of infantile heamangioma in our set-up.

Objective of this study

- To find out the incidence of infantile hemangioma in Bundelkhand region.
- To document the efficacy of oral Propranolol for the treatment of infantile hemangioma.
- Ascertain safe and effective dosage and regimen of Propranolol administration.

METHODS

This Present study was conducted from May 2016 to Nov 2017 after obtaining Ethical permission from Institutional Ethics committee of MLB Medical College, Jhansi, Uttar Pradesh, India. All new patients who were presented with a diagnosis of Infantile Hemangiomas (proliferative phase) were admitted to the Department of Surgery and Pediatrics, M.L.B. Medical College, Jhansi were enrolled into the study. Details of patients were recorded in working proforma.

Detailed examination of lesion were done and dimension of the lesions were recorded. Detailed clinical examination and relevant investigations of every child was done by pediatrician.

Inclusion criteria

All hemangiomas in fit healthy children (male/female) less than 24 months of age.

Exclusion criteria

- Cardiovascular anomalies (History/Examination)
- Lower respiratory tract infections
- Asthma
- Complicated hemangiomas requiring surgical/ alternative medical therapy

Study procedures

- Patients having confirmed hemangiomas after clinical and/ or radiological diagnosis were recruited and admitted for initiation of Oral Propranolol 1 mg/kg/day in two divided therapy for 5 days under the observation of Pediatrician.
- Full pre-treatment cardiovascular workup was done and suspected anomalies were referred to the cardiorespiratory physicians for further evaluation and treatment.
- Follow up was done every four weeks at the Plastic Surgery Outpatients Clinic and if oral Propranolol was well tolerated, it was prescribed at a dose adjusted for weight.
- Oral Propranolol treatment was continued till the age of $1^{1/2}$ years (entire proliferative phase).

Measurement Tools Used

- A clinical assessment was made at each visit to the Outpatients Clinic (every four weeks).
- Photographic documentation was done on every visits: Patient was thoroughly examined by pediatrician for any adverse drug reactions on every follow-up visits.

RESULTS

During the study Period, out of 40 Patients it was observed that 32 Patients was in the Age group of 0-6 months (80%) followed by patients in the Age group of 7-12 months (20%) while no patients was seen between age group of 13-18 months and 19-24 months as shown in Table 1.

Table 1: Distribution of age group.

Age group (in months)	No of patients	Percentage
0-6	32	80.00%
7-12	8	20.00%
13-18	0	00.00%
19-24	0	00.00%

During the study Period, out of 40 Patients it was observed that 22 Patients was female while 18 patients were male as shown in Table 2.

Table 2: Distribution of sex.

Sex	No of patients	Percentage
Male	18	45%
Female	22	55%

In our study it was observed that 36 Patients (90%) had single lesions while only 4 patients (10%) had multiple lesions as shown in Table 3.

Table 3: Distribution of number of lesions.

Numbers of lesions	No of patients	Percentage
Single	36	90%
Multiple (>1)	04	10%

In our study, out of 40 Patients it was observed that 32 Patients (80%) presented with reddish colour of lesion followed by 4 patients (10%) with brownish and skin colour each as shown in Table 4.

Table 4: Colour of lesion.

Colour of lesion	No of patients	Percentage
Reddish	32	80%
Brownish	4	10%
Skin Colour	4	10%

In this study, 18 Patients (45%) had lesion at craniofacial site followed by 8 Patients (20%) near the trunk while Patients having lesions at more than one site was 4(10%) shown in Figure 1.

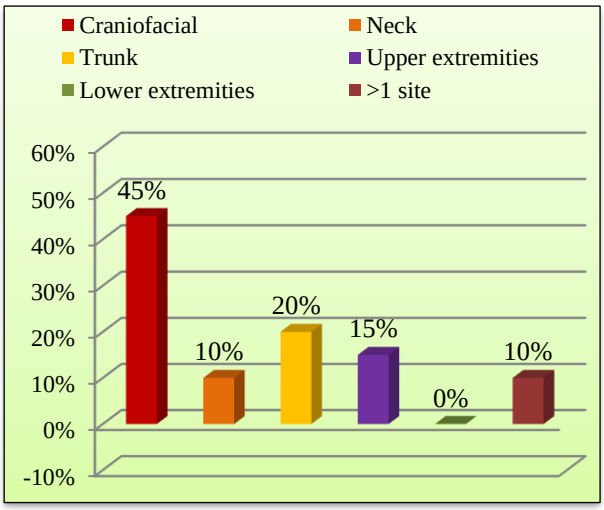

Figure 1: Distribution of site.

In our study, it was observed that 26 Patients (65%) had 0-3 cm size of lesion followed by 10 Patients with 4-6 cm size of lesion while 04 Patients had 7-9 cm size of lesions shown in Table 5.

Table 5: Distribution of size of lesion (maximum diameter).

Size of lesion (in cm)	No of patients	Percentage
0-3	26	65.00%
4-6	10	25.00%
7-9	04	10.00%
>9	00	00.00%

Table 6: Distribution of gestational age.

Gestation Age	No of patients	Percentage
Preterm	26	65.00%
Term	14	35.00%

In our study it was found that 18 patients (45%) presented hemangioma within 0-7 days after birth followed by 08 patients (20%) within 8-15 days after birth, 04 patients (10%) within 22-30 days after birth while 08 patients (20%) presented hemangioma after 30 days of birth as shown in Table 7.

Table 7: Age of presentation of hemangioma for the first time.

Age group (in days)	No of patients	Percentage
0-7	18	45.00%
8-15	08	20.00%
16-21	00	00.00%
22-30	04	10.00%
>30	02	05.00%
<30	08	20.00%

During the study authors observed that All the patients i.e. 40 (100%) responded to our treatment as shown in Table 8. The results were compared by clicking the Photographs before and after the treatment.

Table 8: Distribution of response (size, colour, consistency) of treatment.

Response of Treatment	No of patients	Percentage
Yes	40	100%
No	00	00.00%

DISCUSSION

Infantile Hemangioma (IH) is a benign neoplasm that commonly develops in neonates within their first few months of life. These vascular tumors are more common in Caucasians, and girls are three to five times more likely than boys to have a hemangioma. Most IHs undergo rapid initial proliferation beginning in the first few weeks of life and continuing over several months followed by involution that begins in the last few months of the baby's first year.

Most hemangiomas do not require any treatment; however, a small number do require treatment because of complications potentially caused by the hemangioma. Sometimes treatment is needed if the hemangioma is growing too large or if there is a risk of permanent scarring or disfigurement (damage to the appearance). Treatment may also be necessary if the hemangioma is affecting a vital function, such as vision, eating or breathing, or to help with healing when the skin overlying the hemangioma starts to break down; this is called ulceration.

In the past, systemic corticosteroid was regarded as the gold standard for the treatment of complicated haemangiomas. Labreze first reported the use of propranolol for the treatment of a large facial haemangioma in 2008.[5] Propranolol has become the most widely used medication for the treatment of serious complications from hemangiomas. Since then, this is increasingly regarded as the first-line treatment of choice for complicated haemangiomas. However, the literature is lacking in studies examining the role of propranolol in the treatment of all haemangiomas, specifically of quantitative analysis/imaging in response to treatment.

In our study authors found that 32 Patients was in the Age group of 0-6 months (80%) followed by Age group of 7-12 months (20%) while, out of 40 Patients it was observed that 22 Patients was female while 18 patients were male showing female preponderance. In this study, 18 Patients (45%) had lesion at craniofacial site followed by 8 Patients (20%) near the trunk. No lower limb haemangiomas were presented. These findings were in accordance with the study done by Burns AJ et. Al (2009), Mulliken JB (1998), Rolet BA (2008) , Gampper TJ (2002).[6-9] In our study it was observed that 36 Patients (90%) had single lesions while only 4 patients (10%) had multiple lesions. Authors also observed that 26 Patients (65%) had 0-3 cm size of lesion followed by 10 Patients with 4-6 cm size of lesion while 04 Patients had 7-9 cm size of lesions. Similarly authors found that 18 patients (45%) presented hemangioma within 0-7 days after birth followed by 08 patients(20%) within 8-15 days after birth, 04 patients(10%) within 22-30 days after birth while 08 patients (20%) presented hemangioma after 30 days of birth. Not much of literature has been found on no of lesions which may be due to lack of study done.

In this study, authors observed that 32 Patients (80%) presented with reddish colour of lesion followed by 4 patients (10%) with brownish and skin colour each. During the study Period authors found that 26 Patients had taken pre-term birth while 14 patients had taken birth at term which was contradictory to study done by S. Laranjo et al.(2013).[10] In our study authors observed that all the patients i.e. 40 (100%) responded to our treatment. In our experience propranolol appears to be a useful treatment for severe or complicated infantile hemangiomas, achieving a rapid and significant reduction in size. authors observed propranolol was equally effective in both segmental and non-segmental infantile hemangiomas and in those beyond the proliferative phase. These findings were in concordance with study done by S. Laranjo et al.(2013).[10]

Current treatment options for complicated hemangiomas include various medical or surgical modalities. Till recent times the main stay of treatment for infantile hemangiomas was corticosteroids. Only in complicated or refractory hemangioma cases have other treatment modalities been considered, such as chemotherapeutic agents (vincristine, interferon-alpha), laser therapy, surgery or a combination of these, and, most recently, Propranolol. Each treatment option has limited therapeutic benefit, with its own side effects and risks. However, in the past three years there have been more than 120 reports of the efficacy of oral beta-blockers, usually propranolol, as a highly effective therapeutic option for infantile hemangioma and its complications.[11-14] Furthermore, it has been demonstrated that propranolol therapy is superior to oral corticosteroid treatment, the former standard therapy for infantile hemangioma, and should be considered the first line agent given its safety and efficacy.[15] Possible explanations for the therapeutic effect of propranolol on hemangiomas include vasoconstriction by decreasing the release of nitric oxide, which is immediately visible as a change in color, associated with palpable tissue softening. Other suggestions are down regulation of pro-angiogenic signals such as VEGF, bFGF, MMP-9 and HBMEC, and induction of apoptosis in proliferating capillary endothelial cells.[16,17]

CONCLUSION

In this study, oral propranolol was found to be a simple and effective treatment modality for haemangiomas, with a significant objective regression noted. At the MLB Medical college, jhansi it has become the first-line treatment of all haemangiomas with a safe adverse effect profile, as well as being very cost-effective. However, careful patient selection is important for avoiding any deleterious effects of propranolol and ensuring good compliance with treatment.

In conclusion, a better understanding of the mechanisms of propranolol induced regression of infantile hemangiomas will provide opportunities to design even more successful therapies. Meanwhile, propranolol appears to be a uniquely effective and safe therapy for infantile hemangiomas, including in the post-proliferative phase, and should be considered the first line therapy in this setting. Finally, the improvement of long-term aesthetic sequelae of early propranolol intervention is the ultimate goal.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Hoornweg MJ, Smeulders MJ, Ubbink DT, 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.
2. Keller RG, Patel KG. Evidence-based medicine in the treatment of infantile hemangiomas. Facial Plast Surg Clin North Am. 2015;23(3):373-392.
3. Shayan YR, Prendiville J, Goldman RD. Use of propranolol in treating hemangiomas. Can Fam Physician. 2011;57(3):302-303.
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. Pediatr. 2016 Oct;138(4):e20160353.
5. Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus Corticosteroids in the Treatment of Infantile Hemangioma: A Systematic Review and Meta-Analysis. Plast Reconst Surg. 2013:131(3).
6. Burns AJ, Navarro JA, Cooner RD. Classification of vascular anomalies and the comprehensive treatment of haemangiomas. Plast Reconstr Surg. 2009;124(1):69e-81e.
7. Mulliken JB, Young AE. Vascular Birthmarks: Hemangiomas and Malformations. Philadelphia: Saunders. 1988:24-103.
8. Rolet BA, Swanson EA, Frieden IJ, Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. J Pediatr. 2008;153(5):712-15.
9. Gampper TJ, Morgan RF. Vascular Anomalies: Hemangiomas. Plast Reconst Surg. 2002:110(2):572-86.
10. Laranjo S, Costa G, Paramés F, Freitas I, Martins JD, Trigo C, et al. The role of propranolol in the treatment of infantile hemangioma. Sociedade Portuguesa de Cardiologia. Published by Elsevier España. 2013:290-5.
11. 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. Pediatr. 2009;124(3):423-31.
12. Celik A, Tiryaki S, Musayev A Kismali E, Levent E, Ergun O. Propranolol as the first line therapy for infantile hemangiomas: preliminary results of two centers. J Drugs Dermatol. 2012;11(7):808-11.
13. NeriI, Balestri R, Patrizi A. Hemangiomas: new insight and medical treatment. Dermatol Ther. 2012;25(4):322-34.
14. Phillips CB, Pacha O, Biliciler-Denkta G, Hebert AA. A review of beta antagonist treatment for infantile hemangioma. J Drugs Derma-tol. 2012; 11(7):826-9.
15. Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multi center retrospective analysis. Arch Dermatol. 2011; 147(12):1371-6.
16. Leaute-Labze C, Taieb A. Efficacy of beta blockers in infantile capillary haemangiomas: the physiopathological significance and therapeutic consequences. Ann Dermatol Venereol. 2008; 135(12): 860-2.
17. Léauté-Labrèze C, De La Roque ED, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Eng lJ Med. 2008; 358(24): 2649-51.

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