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Surgery

# COMPARATIVE STUDY OF TREATMENT OF HAEMANGIOMAS WITH ORAL PROPRANOLOL AND CORTICOSTEROIDS.

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**ABSTRACT** Infantile Haemangiomas are the most common vascular lesions of the infancy. Most of the infantile hemangiomas involute by its own but require years. One should opt the treatment of the infantile hemangioma before the development of the long-term memory and self-esteem. Before the emergence of the treatment of hemangiomas with propranolol infantile hemangioma were treated with the steroids. Treatment of the infantile is associated with many side effects. Though the treatment of hemangioma with propranolol has some theoretical side effects practically these are not as severe as steroids. Its author's observation that due to socio-economic constrains, the regular follow up is uncommon in India. In such situation, the treatment with the steroids can be hazardous. Current study concludes that the treatment of the hemangiomas (both in proliferative and nonproliferative phase) with propranolol has better results compared to the steroids.

**KEYWORDS :** Adverse effects, growth phases, lesion distribution

**Introduction:**

Infantile Haemangiomas are the most common vascular lesions of the infancy [1]. Treatment of the haemangiomas with the use of oral propranolol started in 2008 [2]. Since there are no significant side effects as compared to the use of steroids, [3], there is the number of studies and case reports regarding the use of oral propranolol for the treatment of haemangioma, but very few studies were done in Indian healthcare set-up. This study is the attempt to compare the treatment of the haemangiomas with oral steroids, and oral propranolol.

It is authors experience that the people seeking treatment in government hospitals in India are usually from poor socio-economic status. These patients are typically referred from primary practitioners. Also, there is the general belief among general Practitioners that these lesions are self-healing [4]. Because of above reasons, these patients usually present late. This study also tries to evaluate whether there is any effect of the time of commencement of treatment and response.

**Materials and methods:**

***Study Design:***

The present study was carried out in the Department of General Surgery at GMC, Nagpur from July 2012 to November 2014. Approval from hospital ethics committee was taken to conduct this study. Patients were enrolled after obtaining written, informed consent from the patients and patient's parents/guardian (for minor patients). Universal sampling method was used for enrolment of patients to study

***INCLUSION CRITERIA:***

All patients with haemangioma diagnosed clinically or diagnosed after use of necessary investigations.

***EXCLUSION CRITERIA:***

Patients with haemangiomas

- Previously treated with residual lesions.
- with recurrence
- with visceral hemangiomas
- who didn't give consent

Demographic data, clinical history, physical findings were recorded. Patients in whom the diagnosis was not definite were subjected to further investigations like local USG and color Doppler studies, MRI, angiography (either one or multiple) till the exact diagnosis of the lesion was made.

The haemangioma sizes were classified into small (>0-3 cm), medium (> 3-6 cm) and large (>6-9). Depending on diagnosis and age at presentation, management is decided.

**Conservative**

Small, uncomplicated, easy to follow up lesions were managed expectantly.

Medium size and large size lesions (>6-9 cm size), lesions with complications and request of parents for treatment were the reasons for medical management.

***Medical therapy***

**a) Oral Corticosteroids:**

Prednisolone 2mg/kg/day (OD) given for six weeks and gradual tapering was done afterward. Prednisolone 2 mg/kg was given on alternate days for four weeks. Then 1 mg/kg was given on alternate days for 15 days. Afterwards, 0.5 mg/kg was given on an alternate day for one week. Treatment was stopped after 13 weeks of treatment. Follow up visit was mandatory after four weeks for assessment of any complications. If any complications appeared (like cushingoid features), then medication was tapered and stopped.

**b) Oral Propranolol:**

After a careful history and physical examination to exclude any reactive airway or cardiac disease, baseline heart rate and blood pressure were obtained. Propranolol was started at 2 mg/kg/day once a day. Heart rate and blood pressure were monitored before and throughout dose escalation. Since most patients receiving treatment for haemangiomas were infants, it was rare that such patients carry the diagnosis of asthma. Therefore, parents counseled to stop the medication if the infants develop wheezing of any kind, including in the setting of a viral illness. Parents were informed about risks of hypoglycemia and advised to feed infants every 2-4 hours. Patients were given oral propranolol at the dose of 2 mg/kg/day for eight months or till the lesions diminished.

**C) Surgical Excision:**

Surgical treatment was considered in patients with airway obstruction, complications such as ulceration, bleeding and superficial localized lesions in older children (age > 11years) which are unresponsive to medical management. These patients were followed up for recurrence.

**Follow up**

Follow up was done every 4- 6 weekly. Any decrease in the size of the lesion, fainting of color/redness, appearance of islands of skin was carefully noted. After completion of treatment follow up response was graded by scale given by Sloan, Reinisch, and Nichter [5].

| | |
|---|---|
| Excellent | - Near total disappearance |
| Good | - Greater than 50 percent reduction in volume |
| Fair | - Definite decrease in size, but by less than 50% |

Poor - Little or no decrease in size

The response rate, as well as complications of both treatment, i.e., oral propranolol and oral steroid, were compared.

The response of oral propranolol versus oral steroid was compared in patients of haemangioma using Mann-Whitney U and Wilcoxon W test. p-value < 0.05 was considered statistically significant.

**RESULTS:**

After application of inclusion and exclusion criteria, total 81 patients were enrolled in the study. F: M ratio of vascular anomalies is 1.3:1

The total number of patients in proliferative phase was 15. Most common age group affected was between the age of >1 month to 1 year. (table 1)

**Table 1. AGEWISE DISTRIBUTION OF HAEMANGIOMAS**

| Age in months/years | Number (78) | Percentage |
|---|---|---|
| 1 month | 9 | 11.11 |
| >1 month-1 year | 25 | 30.86 |
| 1-4 years | 19 | 23.45 |
| 4-8years | 5 | 6.17 |
| 8-12 years | 4 | 6.17 |
| >12 years | 6 | 9.87 |

Head, neck and face region was most commonly involved (46.9%). Next most common involvement was seen in extremities (29%), Trunk (14%), visceral (9%) and genitalia involvement were least common (2%). (Table 2)

**Table2. Distribution of the lesions.**

| Site | HNF (38) | Percentage |
|---|---|---|
| Lip | 8 | 21.05 |
| Periocular | 4 | 10.52 |
| Parotid | 2 | 5.26 |
| Nose+ perinasal | 1 | 2.63 |
| Ear+ periauricular | 1 | 2.63 |
| Face+ perioral | 5 | 13.15 |
| Oral cavity | 1 | 2.63 |
| Forehead | 4 | 10.52 |
| Cheek | 4 | 10.52 |
| Chin | 5 | 13.15 |
| Scalp | 5 | 13.15 |

Haemangioma lesions were most commonly present on lips (Table 3).

**Table 3. DISTRIBUTION OF HAEMANGIOMA CASES AND TREATMENT GIVEN**

| Treatment | Number (78) | Percentage |
|---|---|---|
| Oral PPL | 32 | 39.50 |
| Oral Steroid | 14 | 17.28 |
| Surgery | 8 | 9.87 |
| Observation/conservative management | 24 | 29.62 |

Oral propranolol was given for 32 (39.50%) patients, 14 (17.28%) patients received oral steroid, 8 (9.87%) patients underwent surgery. Conservative management or observation was done in 24 (29.62%) patients with infantile haemangiomas having the very small lesion and age less than four months

(table 4).

**Table 4. FOLLOW UP RESPONSE IN HAEMANGIOMAS**

| Response | Propranolol (32) | Percentage | steroid (14) | Percentage | Surgery (8) | Percentage |
|---|---|---|---|---|---|---|
| Excellent | 4 | 12.5 | 1 | 7.14 | 7 | 87.5 |
| Good | 20 | 62.5 | 6 | 42.85 | 0 | 0 |
| Fair | 7 | 21.9 | 2 | 14.28 | 0 | |
| Poor | 1 | 3.1 | 5 | 35.71 | 1 | 12.5 |

**P value =0.03 (<0.05)**

No adverse effects were seen in patients treated with propranolol. Response with propranolol was good-excellent in 24(75%). Excellent response was observed in 4(12.5%), the good response was seen in 20 (62.5), Fair response (<50% decrease) was seen in 7 (21.9%) with oral propranolol. Only one patient had the poor response (3.1%). Patients presented with ulceration were given propranolol and responded well. ulcers healed within the time span of 3 weeks

The response rate to oral steroid was good in 6 (42.85%) and excellent in 1(7.14%). Response to surgery was excellent in 87.5% and poor in one patient who had the recurrence.

Oral steroids were associated with complications such as cushingoid features (35.71%), hyperglycemia (14.28%), failure to weight gain and lethargy (14. 28%).

Follow up the response of oral propranolol versus oral steroid was compared in patients of haemangioma using Mann-Whitney U and Wilcoxon W test. It was statistically significant with the p-value of 0.03. The before and after treatment photos are shown in fig 1 and 2.

**Figure 1. Ear lobe haemangioma after treatment with propranolol. (complete regression of the lesion).**

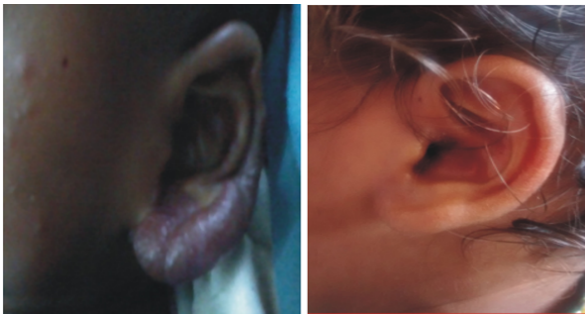

**Figure 2. lower lip hemangioma progressive course with treatment with propranolol.**

**Discussion:**

Propranolol is a nonselective b-blocker with antagonistic action on b1- and b2-adrenergic receptors [6]. Leaute – Labreze first used propranolol for the treatment of the hemangioma[2]. Initially, we decided to use oral propranolol and steroid to use in alternate patients, but with the time treatment with steroids was withheld because patients on steroid developed adverse effects. Afterwards, oral propranolol was used for the treatment.

Out of 14 patients of haemangiomas on oral prednisolone, 5 (35.71%) showed cushingoid features, 2 (14.28%) showed characteristics of hyperglycemia and 2 (14.28%) patients showed the failure to weight gain and lethargy. Michelle Bennet in 2001 reviewed ten studies which used oral corticosteroids for the treatment of the haemangiomas [7]. He noted that the incidence of side effects of the oral corticosteroids was in the range of 27% to 35%. Reported adverse effects were cushingoid features, increased infections, growth delay, irritability, gastrointestinal upsets, and osteoporosis. The side effect profile of current study was similar these studies.

Bradycardia, hypotension, and hypoglycemia are well-known side effects of the beta-blockers [8]. Asthma is the contraindication for the use of Propranolol [6], and it should not be used in active bronchiolitis. In our study, our patients tolerated the therapy well, and none of the patients precipitated asthma. None of our patients developed hypoglycemia, we think that it might be because of instructions were given to mothers of patients about feeding every 2-3 hourly, we recommend that instructions about repeated feeding should be given to

infants and pediatric age group to nullify the theoretical risk of hypoglycemia.

We also recommend that every patient or parents of patients if infants on propranolol treatment should be taught about warning signs of hypoglycemia. None of our patients developed hypotension. Electrocardiogram and complete cardiac examination should be done before starting of the propranolol treatment.

The response of our studies is similar to the studies done by Buckmiller et al. and Qiang Xiao [8, 9]. The response of the propranolol was variable, and further research is required to study the variable response with the propranolol. Out of 32 patients included in our study, four patients had the complete response with treatment, 20 (62%) patients had 50- 80 % reduction, 7(21%) patients had the response which was less than 50%. So there is the definite need to formulate the other modality of treatment which can be used either before or after or in combination with the treatment with oral propranolol.

Phases of growth of the infantile haemangioma involve early proliferative phase, late proliferative phase, plateau and involuting phase. [4] It is considered that the treatment of the infantile haemangioma is most effective if it is started in early proliferative phase [10]. According to Bowen who observed 169 lesions till the end of the eighth year and found that only 16 patients remained in the study whose lesions weren't healed rest of the patient were almost cured [11]. Similar results were found in the study done by Wallace who observed that more than 90% of the lesions were healed at the end of the 7th year [11]. But recently Couto et al. suggested that the haemangiomas beyond 3.5 years should be considered as non-involuting, and surgical treatment should be considered for the same. The reasons he quoted for the surgical management were that "Infantile haemangiomas often do not completely resolve and following involution children may be left with fibrofatty tissue, damaged skin, destroyed anatomical structures and telangiectasias." He also suggested that treatment of the haemangiomas should be done before the development of the long-term memory and self-esteem[12]. In our study, only 15 patients who were started on treatment were in proliferative phase. In rest 17 patients 11 patients had the good response, and two patients had excellent response. This shows that response with treatment with propranolol is seen in both proliferative and non- proliferative phase of the haemangioma. Considering above studies, we recommend that treatment of the hemangiomas with propranolol should be started as early as possible preferably in proliferative stage and should be given before reconstructive surgery to reduce the lesion to minimum size.

**Conclusion:**

If proper precautions are taken, then there are no severe side effects associated with treatment with oral propranolol. In Indian scenarios, especially the population seeking treatment to government tertiary care centers are from poor economic class. Many times, these patients are not able to follow up regularly. Considering the adverse side effects associated with treatment with steroids and inferior results compared to the oral propranolol, we recommend that every patient of IH should be started on treatment with oral propranolol.

**Limitations:**

In this study, we haven't focussed on the side effect profiles like increased sleepiness, restless sleep, gastroesophageal reflux, allergic rash, respiratory syncytial virus exacerbation, Gastrointestinal problems.

Possibility of recurrence of the hemangioma after therapy was not studied.

## REFERENCES


1. Kilcline, C., & Frieden, I. J. (2008). Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatric dermatology, 25(2), 168-173. Doi: 10.1111/j.1525-1470.2008.00626.x
2. Léauté-Labrèze, C., de la Roque, E. D., Hubiche, T., Boralevi, F., Thambo, J. B., & Taïeb, A. (2008). Propranolol for severe hemangiomas of infancy. New England Journal of Medicine, 358(24), 2649-2651. Doi: 10.1056/NEJMc0708819
3. Izadpanah, A., Izadpanah, A., Kanevsky, J., Belzile, E., & Schwarz, K. (2013). Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. Plastic and reconstructive surgery, 131(3), 601-613.Doi: 10.1097/PRS.0b013e31827c6fab
4. Luu, M., & Frieden, I. J. (2013). Haemangioma: clinical course, complications and management. British Journal of Dermatology, 169(1), 20-30.Doi: 10.1111/bjd.12436
5. Sloan, G. M., Reinisch, J. F., Nichter, L. S., Saber, W. L., Lew, K., & Morwood, D. T. (1989). Intralesional corticosteroid therapy for infantile hemangiomas. Plastic and reconstructive surgery, 83(3), 459-467.
6. Tripathi KD. Essentials of medical Pharmacology. 5th ed. New Delhi: JAYPEE brothers medical publishers limited; 2008. 127-37 p.
7. Bennett, M. L., Fleischer Jr, A. B., Chamlin, S. L., & Frieden, I. J. (2001). Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. Archives of dermatology, 137(9), 1208-1213. Doi: 10.1001/ archderm. 137.9.1208
8. Buckmiller, L. M., Munson, P. D., Dyamenahalli, U., Dai, Y., & Richter, G. T. (2010). Propranolol for infantile hemangiomas: early experience at a tertiary vascular anomalies center. The Laryngoscope, 120(4), 676-681. Doi: 10.1002/lary.20807
9. Xiao, Q., Li, Q., Zhang, B., & Yu, W. (2013). Propranolol therapy of infantile hemangiomas: efficacy, adverse effects, and recurrence. Pediatric surgery international, 29(6), 575-581. Doi: 10.1007/s00383-013-3283-y
10. Chang, E. I., Chang, E. I., Thangarajah, H., Hamou, C., & Gurtner, G. C. (2007). Hypoxia, hormones, and endothelial progenitor cells in hemangioma. Lymphatic research and biology, 5(4), 237-244. Doi: 10.1089/lrb.2007.1014
11. Bowers, R. E., Graham, E. A., & Tomlinson, K. M. (1960). The natural history of the strawberry nevus. Arch Dermatol, 82(5), 667-680. Doi: 10.1001/ archderm. 1960. 01580050009002
12. Couto, R. A., Maclellan, R. A., Zurakowski, D., & Greene, A. K. (2012). Infantile hemangioma: clinical assessment of the involuting phase and implications for management. Plastic and reconstructive surgery, 130(3), 619-624. Doi: 10.1097/PRS.0b013e31825dc129