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A prospective study of treatment of problematic infantile hemangiomas with propranolol and its outcome.

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Abstract :
Aims: *To study the use of propranolol as a single therapy in problematic infantile hemangioma and its outcome.*
Methods: *Single institutional prospective study of patients of problematic infantile hemangioma treated with propranolol between January 2010 to December 2013. Assessment was done by change in colour , redness ,size and parental satisfaction. Outcome was defined in terms of complete, excellent, good/partial and no response.*
Results: *23 girls and 9 boys with infantile hemangioma were initiated treatment with propranolol at the mean age of 9.9 months(range 2-48 months) for a mean duration of 21 months(range 8-35 months). Head and neck was the most common site(75%). Complete/excellent response was seen in 20 patients(62.5%), good/partial response in 9(28.13%) and no response in 3 patients(9.38%). Rebound was seen in 2 patients. 4 patients showed increased sleepiness.*
Conclusions: *Propranolol was safe, effective and should be the first line therapy in problematic hemangioma. Adjuvant therapy may still be needed in residual lesions and in partial response. Small superficial hemangioma showed excellent response. Hemangioma with deep components have high risk for rebound and probably need longer treatment*
Keywords: *Propranolol, problematic infantile hemangioma, outcome*

I. INTRODUCTION

Infantile hemangioma is probably the most common benign tumor in infants.[1] Though majority show spontaneous involution, approximately 10% are problematic i.e may ulcerate, bleed, there may be chances of disfiguration, may involve vital structures due to which may be life or function threatening. [2]

Various treatment options are available: 1) systemic corticosteroids which was commonly used in the past, 2) oral propranolol emerging as the frontline therapy, 3) recent use of topical timolol has been reported in small, superficial hemangioma and 4) other available options like laser therapy, intralesional steroids, surgical excision,etc. [3]

Infantile hemangioma is believed to be a benign tumor due to hyperplasia of vascular endothelial cells with various theories to explain vasculogenesis and angiogenesis. After an initial latent period, it shows proliferative phase, plateaus and then starts involution.

Incidental use of propranolol in infantile hemangioma was first reported in the landmark paper in New England Journal in 2008. [4] Since then it has emerged as the front line therapy with US FDA approval. The mechanism of action is believed to be vasoconstriction, apoptotic signaling and downregulation of vasculogenic proteins. [5]

Certain issues remain – regarding standardization of initial dosing for efficacy, the duration of treatment and follow-up, when to stop the treatment and also how to deal with the incidence of rebound growth after stoppage of treatment. Also though systematic analysis have proven its efficacy and safety, conclusive evidence in the form of experimental models to prove its status as first line therapy is awaited. Studies are trying to find answers to why there is partial or no response in some and whether it is related to the age and stage of starting the treatment.

Therefore , though now an accepted and approved mode of treatment, more prospective studies are needed in India(where there is a relative paucity of such studies on propranolol) with long follow up to address the above issues in the near future.

II. MATERIALS AND METHODS

Prospective study was carried out at our institution between the period January 2010 to December 2013 with the approval from the ethical committee of the institution. All patients with problematic infantile hemangioma were included in the study with informed consent obtained from both the parents. Operative definition of problematic hemangioma was those hemangiomas ulcerating or bleeding, may disfigurate or

involving vital structures due to which may be life or function threatening. Infants with cardiovascular disorders, bronchospasm, hypoglycaemia were excluded from the study. Preoperative evaluation was done by complete blood investigations, USG with Doppler and echocardiography evaluation. Propranolol was administered with the starting dose of 2 mg/kg/day given in 2 divided doses. Blood pressure and heart rate were monitored during the first 4hr of treatment. In the absence of side effects, treatment was continued at home and the child was re-evaluated after 2 weeks and then every month. Parents were counselled about the possible side effects. The patients were followed by serial photographs taken during the course of treatment and wherever possible by ultrasonography in the institution to evaluate the therapeutic response. The variables noted in the course of treatment were: age, sex, location, the dose , duration of treatment, follow up data and adverse effects if any. Clinical evaluation at follow up and serial photography were done to assess the response to oral propranolol therapy in terms of change in colour and redness. Wherever possible ultrasonography at the institution was repeated at 60 days to measure the maximum dimension of the hemangioma to assess the response in terms of change in size. For assessment of patients with eyelid involvement, repeated ophthalmological consultations were done.Thus assessment was done by the change in colour, redness and size and parental satisfaction at follow up. Outcome was defined in terms of complete response, excellent response (>75% reduction in size), good/partial response (>50% reduction in size) or no response.

III. RESULTS

There were 32 patients with problematic infantile hemangioma treated with oral propranolol between Jan 2010 and Dec 2013 and subsequently followed upto Dec 2016. Out of 32 patients, 23 were girls and 9 boys. Male : female ratio was 1:2.55. The mean age of initiation of treatment was 9.9 months (range 2-48 months). The mean age of duration of treatment was 21 months (8-35 months).

The various locations of hemangiomas were as follows:

(A)Head and neck was the most commonly involved site in 24 patients(75%): cheek (n=10), periorbital region (n=7), parotid region (n=5), lip (n=4),neck(n=4),nose(n=3),ear(n=2),glabella(n=2), submandibular region(n=1). Multifocal hemangioma in head and neck regions was found in 12 patients with synchronous involvement of two sites together in 9 patients and 3 sites together in 3 patients

(B) Trunk was involved in 3 patients

(C) Extremities (thigh region) was involved in 3 patients

(D) Perineum alone in 2 patients and together with gluteal region in another patient.

Overall there was multifocal involvement across anatomical regions in one patient (neck and trunk).

Regarding the nature of problematic hemangiomas: 12 patients (37.5%) were ulcerative, 4 patients (12.5%) bleeding , 2 patients(6.25%) had ptosis. 2 patients had presented after having already received oral coticosteroids prior to propranolol treatment.

An oral dose of propranolol was continued at 2mg/kg/day divided two times daily in 18 patients whereas in 14 patients, dosage was increased to 3mg kg/day after 2 weeks to maximize efficacy.

Nearly every patient treated with oral propranolol displayed some improvement of their lesion. Complete or excellent response was seen in 20 patients (62.5%) and required no additional therapy. 9 patients demonstrated good/partial response and received adjuvant therapy to complement their treatment. No response was seen in 3 patients and required alternative modality of therapy.

Rebound was seen in 2 patients after complete response with a mean follow up of 4.5 months. Both again showed complete regression on oral propranolol therapy.

4 patients experienced minor adverse effect as increased sleepiness (n=4, 12.5%).

Table 1: Summary of the result analysis of our series

VARIABLES	NUMBER
No of patients	32
Sex distribution Females Males Female : male ratio	 23 09 2.55:1
Mean age of initiation of treatment	9.9 months (range 2-48 months)
Mean duration of treatment	21 months (range 8-35 months)
Location (a) Head & neck (b) Trunk (c) Extremities	 24/32(75%) 03/32(9.38%) 03/32(9.38%)

(d) Perineum	02/32 (6.25%)
Multifocal	12/32(37.5%)
Problematic infantile hemangioma: complications:	
(a) Ulcerative	12/32(37.5%)
(b) Bleeding	04/32(12.5%)
(c) Functional risk	02/32(6.25%)
Composition:	
Superficial :	24/32(75%)
Deep components:	08/32(25%)
Response	
(a) No response	03/32(9.38%)
(b) Good/partial response (>50% of reduction of size of lesion)	09/32(28.13%)
(c) Excellent response (>75% of reduction of size of lesion) or Complete response	20 (62.5%)
Rebound	02/32 (6.25%)
Adverse effect(s):	
(a) Serious adverse effect(s)	None
(b) Non-serious adverse effect(s)	
Increased sleepiness	04/32 (12.5%)

IV. DISCUSSION

Infantile hemangioma is probably the most common benign soft tissue tumor in the infants. [1] Though most show spontaneous involution, approximately 10-15% are problematic and require treatment. [2]

Prevalence in neonates is ~4-5% with female (2-3 times higher) predominance and an increased incidence in premature and low birth weight babies. [6,7]

No single hypothesis has been able to describe the pathogenesis of infantile hemangioma. Hypoxic stress is believed to induce the upregulation of vasculogenic and angiogenic peptides. [8] After an initial latent period of 1-3 weeks, hemangiomas show characteristic proliferative growth usually rapid in the 1st 3 months, plateau usually till 1 year of age (in rare cases upto 2 years) and then start involuting till 5-7 years. Approximately 10-15% are problematic i.e. may be ulcerative, bleeding, disfigurating ,close to vital structures or life or function threatening and form the indications for treatment. Diagnosis is clinical with confirmation by imaging. [2]

Superficial infantile hemangioma is confined to the skin and may appear as elevated red papule, nodule or plaque whereas deep infantile hemangioma has subcutaneous location having extended to adipose tissue and may appear as bluish nodules. Most superficial hemangiomas are evident by 1-4 weeks of age whereas deep hemangiomas often present late at 2-3 months of age. Regional or segmental infantile hemangioma and deep infantile hemangioma may continue to proliferate till 12 months of age and in rare cases upto 24 months. Regional or segmental hemangioma are more likely to be problematic. Hemangioma more than 5cm in size, segmental located in face, periorbital, perioral,perineal regions are associated with high risk of functional compromise or disfigurement and permanent residual damage. [9]

The various treatment options are :

Oral propranolol emerging as the 1st line systematic therapy.

Systematic corticosteroids: previously the mainstay of treatment but now less preferred.

Recent use of topical timolol esp in small superficial hemangioma.

Others : laser therapy, intralesional steroids, surgical excision. [3]

Propranolol was invented by Sir James W Black as the 1st clinically useful non selective b blocker for the management of angina pectoris. [10] Leau- Labreze et al 1st reported the incidental finding of regression of hemangioma in children treated with propranolol for cardiac and renal conditions. [4] From the current understanding , the mechanism of action of propranolol is that it induces vasoconstriction, apoptosis and

downregulation of angiogenic and vasculogenic peptides chiefly vascular endothelial growth factor(VEGF) and basic fibroblast growth factor (bFGF). [5]

Malik and Rao et al in a prospective study concluded that propranolol had a consistent , rapid therapeutic effect compared to prednisolone : the combination of the two had a comparable but not higher efficacy than propranolol and that prednisolone had higher number of systemic complications. [11] In another RCT propranolol was shown to have better efficacy and fewer side adverse effects than systemic corticosteroids. [12,13,14]

Chan et al in a recent RCT reported the potential of topical timolol to be an effective topical agent for small superficial infantile hemangioma thus avoiding systemic effects. [15] But there is concern of transcutaneous or transconjunctival resorption leading to systemic side effects due to 1st pass effect. [16]

Laser therapy though still widely used, a prospective RCT didn`t find it any better than spontaneous involution. [17] Another study while comparing it with propranolol, found involution to be more rapid with propranolol. On the other hand, a small scale clinical study found the efficacy of propranolol at the administered dose of 2mg/kg/day to be higher than laser therapy and cryosurgery. [18] But laser therapy may still be used as adjuvant therapy in partial response or treatment of residual lesion even in excellent or complete response.

In probably the largest systematic review of oral propranolol in the treatment of infantile hemangioma which included studies reported in English literature where at least 10 patients were treated with oral propranolol for infantile hemangioma reported at least one adverse effect or planned to report so, 83 studies met the inclusion criteria out of which only 18 are prospective studies with at least 30 patients treated with oral propranolol. [19]

In India there is a relative paucity of large prospective studies on oral propranolol in infantile hemangioma. We have presented our results alongwith with 3 important Indian prospective studies in a tabular form.

Table 2: Large Indian prospective studies documenting the results of treatment of problematic infantile hemangioma with propranolol and its outcome:

Series	Number	Age of initiation of treatment	mean duration of treatment	Location	Indications	Response	Complications
V. Pandey, A. N. Gangopadhyay 2014[20]	52 pts treated with oral propranolol only	Mean age of initiation 18.3+_ 12.4 months	6.5+_ 3.4 months	1.Head & neck =13 2.Face=13 3. Intraoral=5 4.Trunk =11 5.extremity=8 6.Genitalia=2 Multifocal =8	Ulceration=8 Cosmetic=11 Functional=15 Bleeding=16 Problematic handling=2	1.complete responders =04/52 2.excellent responders =30/52 (56.7%) 3.Partial responders =15/52(28.8%)	Nil
Malik, KLN Rao 2013[11]	30 pts Group A:treated with oral propranolol only B: treated with prednisolone C: treated with both for a minimum of 3 months	Mean age of initiation: A:4.6 (1-8m) B:5.5m (2-8m) C:4.7m (1-8m)	Mean age at the end of treatment : A: 15.3+_ 5.2m B:18.1+_ 4.3m C:15.8+_ 4.1m	A. Head & neck = 20 (66%) Parotid 30% Lip 13.3% Scalp 10% Superficial =16 (53%) Mixed=8 (26.7%) Deep =6 (20%)	Group A: ulceration with bleeding n=1 Group B: tongue hemangioma with feeding difficulty n=1 Group C: ulceration with bleeding (n=2) Ulceration only (n=1)	Mean reduction in size in the 1st 3 months of treatment: A: 35.5%+_ 21.3% B: 21.5%+_ 21.7% C:31.7% +_ 30.3%	A: 2/10 Hypoglycaemia 01 Somnolence 01 B: 09/10 Cushingoid appearance 05/10 GI upset 03/10 Regrowth at the end of 3 week cycle 03/10 C:07/10,

							mostly by prednisolone Cushingoid appearance 06/10 GI upset 04/10 Regrowth 01/10 Infection 01/10
N. Sharma, S.S.Panda, A.Singh, M.Bajpai 2013[21]	A: treated 69 pts with oral prednisolone(n=24) B: treated with oral propranolol (n=22) C: treated with both (n=23)	Mean age initiation of treatment 30.1+_ 9.2 weeks	Mean duration of treatment 14.9+_2.1 weeks			A:no response: 6/24 Partial response 8/24 Good response 10/24 B: no response 10/22 Partial response 7/22 Good response 5/22 C: no response 7/23 Partial response 10/22 Good response 6/23	
Our series	n=32 pts M:F::1:2.55	Mean age of initiation 9.9 months (range 2-48m)	Mean duration of treatment 21 (range 8- 35 months)	(A) Head & neck 24 (B) Extremities 03 (C) Trunk 03 (D) Perineum & gluteal region 02	1)ulceration 12 2)bleeding 04 3)functional risk 02	1) complete or excellent response 20/32 2)good or partial response 09/32 3) no response 03/32	Increased sleepiness 04/32

As reported by the large systematic analysis, oral propranolol was well tolerated with only mild adverse effects in the above named Indian studies. Preoperative screening and assessment is important to exclude patients at risk before planning to administer oral propranolol. Regarding within treatment monitoring of oral propranolol, with a Tmax of 2 hours it is currently sufficient to monitor for vital signs for at least 2 hours during the administration of 1st dose or during each escalation of dose. [19] In our series, only 4 out of 32 patients showed increased sleepiness.

Though studies have reported its efficacy, there is no standardisation on initial dosing of oral propranolol. In the initial years some even reported low dose initiation at 1-1.5 mg/kg/day. The large systematic analysis shows that most large studies initiated oral propranolol at 2-3 mg/kg/day. Most started at 2mg/kg/day and none went beyond 4mg/kg/day. [19] Chavez et al have reported that a dosage of more than 4 mg/kg/day put the pediatric patients at risk for development of hypoglycemic events. [22] We also initiated at 2mg/kg/day in all. 18 patients continued to receive propranolol at 2mg/kg/day whereas in 14 patients with hemangioma in periorbital, perioral , nasal and perineal regions deemed high functional risk as per modified Luu and Frieden risk stratification [9, 23], the dose was increased to 3mg/kg/day to maximize efficacy.

The exact reasons for variability in response is not known but is understood to be due to the variability in tumor composition with the deep component being vital to response and hence the sequelae. [20,24] Also, sometimes stabilisation of growth is mistaken as no response in the subjective assessment of hemangioma.[25]

In most of the patients, response was noted within 2-3 weeks.

In our series, we analyzed the 3 patients with no response individually. 2 patients had unifocal hemangioma in the trunk, had a deep component, presented at 20 months and 24 months of age respectively. Both had received oral propranolol at 2mg/kg/day and showed no regression on 6 months of treatment . Another patient had unifocal hemangioma in left thigh, > 5cm in size, had a deep component, presented at 10 months of age showed no regression even after 6 months of treatment.

In our series, all the small sized (<5 cm) superficial hemangiomas showed excellent or complete response. 8 patients had deep elements out of which 5 showed good response of which 4 were <5cm in greatest dimension.

Propranolol is given for the entire proliferative phase, often for 1 year or longer. Recurrence or rebound is probably due to the proliferative phase continuing more than 12 months especially in infantile hemangioma with deep component and segmental infantile hemangioma. In these cases, probably longer treatment is needed. [26]

Rebound was seen in 2 patients after complete response with a mean follow up of 4.5 months. Both again showed complete regression on oral propranolol therapy.

The various potential adverse effects reported at the recommended dosage for the treatment of infantile hemangioma include (a) serious ones like: hypoglycemia, bradycardia, hypotension, bronchospasm and (b) non serious ones like : sleep disturbance , cold extremities, diarrhea. [27] In our series, 4 patients experienced minor adverse effect as increased sleepiness.

V. CONCLUSION

Use of oral propranolol in problematic infantile hemangioma is cost effective compared to other alternatives and safe with very few adverse effects at the recommended dosage of 2-3 mg/kg/day in divided dosage. Therefore it should be the first line of therapy though experimental models will be needed with long follow up as proof with large well designed prospective studies to corroborate the findings.

Heterogenous behavioural response of infantile hemangioma is due to variability in size, location and composition. Still most patients with problematic infantile hemangioma showed excellent or good response or arrest in proliferation at 2-3 mg/kg/day dosage schedule.

Problematic hemangioma with small sized superficial hemangioma showed excellent or complete response. Adjuvant therapy like laser therapy or surgical excision was needed in partial responders or even in treatment of residual lesions after excellent response. Infantile hemangioma with deep component had higher risk of rebound and probably needed longer treatment due to longer proliferative phase.

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