

Original Research:**A Randomised Controlled Study On Efficacy Of Propranolol, Prednisolone And Propranolol With Prednisolone In Infantile Hemangioma.****Pramod Kumar Mohanty, Jiten Patel, Hiranya Kishor Mohanty, Pradeep Kumar Jena, P.K. Tripathy, R.K. Mohaptra, M.R. Dash, Gadadhar Sarangi.**

Associate Prof. S.V.P.P.G.I.P, Senior Residence, S.V.P.P.G.I.P, Prof. S.V.P.P.G.I.P, Prof & Head S.V.P.P.G.I.P, Assistant Prof. S.V.P.P.G.I.P, Assistant Prof. S.V.P.P.G.I.P, Assistant Prof. S.V.P.P.G.I.P, Retired Prof. and Director Post Graduate Department of Pediatrics, Hi-tech Medical college, Bhubaneswar.

Correspondence to - Dr. Gadadhar Sarangi. "THE CHILD". Ranihat, Cuttack-753001.

Email- drgadadhars@gmail.com

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Citation of article: *Pramod Kumar Mohanty, Jiten Patel, Hiranya Kishor Mohanty, Pradeep Kumar Jena, P.K. Tripathy, R.K. Mohaptra, M.R. Dash, Gadadhar Sarangi* A Randomised Controlled Study On Efficacy Of Propranolol, Prednisolone And Propranolol With Prednisolone In Infantile Hemangioma, New Indian Journal of Pediatrics 2018, 7:3; p. 166-177**Abstract:****Objectives**- To compare the efficacy of oral propranolol, Prednisolone and propranolol with prednisolone in the treatment of infantile hemangiomas and to standardise the dose of propranolol.**Design** – Prospective randomized comparative study.**Setting** – Pediatrics Surgery Department of a Tertiary care hospital.**Study period** – September 2012 to December 2014.**Participants** – Infants below 8 months of age with cosmetically disfiguring or functionally deranging hemangiomas.**Results** – The mean size reduction (%) based on visual Analogue scale for propranolol treated group at 3 months, 6 months, 1 year, and 1.5 years were 58.21±19.50, 71.21±18.35, 85±11.32 and 89.88±10.26 respectively. For the group treated with prednisolone at the same period the size reduction was 36.57±18.97, 46.94±26.84, 66.25±31.21 and 66.64±32.36 respectively. For the group treated with Prednisolone and Propranolol the reduction the above age were 49.99±19.25, 71.07±17.69, 79.19±13.95 and 82.64±10.36 respectively. The side effects are more with prednisolone group and prednisolone with propranolol group.**Conclusion** – Propranolol should be considered as first line

agent in therapy for infantile hemangioma for its safety and efficacy. 2 mg/kg/day in two divided doses considered to be optimal.

Key words – Infantile hemangioma (IH), Propranolol, Prednisolone, Visual Analogue Scale (VAS). Funding – NO external funding, Competing interest – Not stated.**Introduction:**Infantile hemangiomas (IHs) are the most common soft-tissue tumors of infancy, occurring in 4% to 10% of children under 1 years of age, with a clear female predominance (Female:male ratio – 2.5 to 4:1). Multiple lesions are found in 15-30% of patients with infantile hemangiomas.^[1] recognised risk factors for the development of hemangiomas include prematurity, fair skin and female sex. Mothers of patients with IHs are of higher maternal age, have a higher incidence of pre-eclampsia or placenta previa and are more likely to have multiple pregnancies.^[2]**Types of hemangiomas**

IH may be superficial, deep or mixed. They are usually superficial involving the skin and therefore

obvious on physical examination. On occasion, IHs are completely confined to the subcutaneous soft tissues (deep), presenting as a bluish lump with intact overlying skin.^[3] they may also involve superficial and deep tissue (mixed).

IHs can be focal, segmental or indeterminate. Focal hemangiomas are more common and present as localized, raised and tumor-like lesions. Segmental hemangiomas are flat, larger, plaque-like and has a segmental distribution. Indeterminate lesions do not entirely encompass an accepted embryological segment or arise from a single focus and can demonstrate mixed features.

At birth, IHs may not be apparent or may appear as flat circumscribed lesions with telangiectasia vessels on the surface. Approximately 30% have a precursor lesion indicated by the presence of a macule, an area of discoloration or telangiectasia. Within the first weeks of life, IHs enter a phase of rapid growth with superficial and/or deep components, which lasts usually 3 to 6 months and sometimes upto 24 months. A period of stabilization for a few months follows, and spontaneous involution usually occurs in several years. Regression is complete in 60% within 4 years and 76% within 7 years.^[4] Most of the time sequelae are minimal, with residual cutaneous redundancy, fibrous and fatty residues, and telangiectases, which can be treated with late surgery or pulsed-dye laser therapy. Because of this benign, self-limiting course, therapeutic abstention is the rule.

However, 10% of IHs require treatment during the proliferative phase, because of life-threatening locations, local complications, or cosmetic/functional risks.^[5] IHs can be life-threatening when present in upper airways and liver, inducing acute respiratory failure and congestive heart failure, respectively. In addition, they cause at least transient cosmetic disfigurement, which may trigger psychological morbidity first in parents and later in affected children. Hemangiomas in certain anatomic regions are especially likely to cause psychosocial

problems, such as those in the nasal tip, glabella, and cheek.

Treatment options

The conventional approach in complicated cases is to use systemic corticosteroid therapy as first-line treatment and then interferon or vincristine as second- or third-line therapeutic agents. Propranolol has come up as a newer therapeutic agent.

Steroids

Even with high doses (2-5 mg/kg per day) rate of response to systemic corticosteroid therapy (stabilization or incomplete regression, in most cases) range from 30% to 60%, with the effects appearing within the first 2 or 3 weeks of treatment.⁶ Side effects are multiple although mostly transient and limited, such as Cushingoid facies, insomnia, irritability, stunted growth and gastrointestinal symptoms. Some may become much more serious, such as hypertension and hypertrophic obstructive cardiomyopathy. Intralesional corticosteroids used for treating palpebral hemangioma can also lead to central retinal artery occlusion.^[7]

However, oral prednisolone therapy remains one of the most common treatment modalities for proliferating hemangiomas and has been the drug of choice for out patient therapy. Steroids have been shown to be antiangiogenic in a number of in vitro settings. Additionally, steroid may influence capillary vascular tone. While their efficacy is not disputed, children are laibale for complications.^[8,9]

Interferons/Vincristine

Complete response to interferon (either 2 alpha or 2 Beta) at 1-3 U/m²/day has been seen in 40-50% of complicated cases with the first signs of regression appearing after 2-12 weeks of treatment.¹⁰ Frequent side effects include fever and muscular pains at the beginning of treatment. Hematologic and hepatic toxicity, hypothyroidism and neurotoxicity with spastic diplegia and developmental delay may occur. Another recent treatment option is vincristine given at 0.05 mg/kg or 1 mg/m² infusions once a week.

Efficacy is close to 100%, with IH involution beginning at 3 weeks after treatment. Significant side effects include constipation, peripheral neuropathy, hematologic toxicity and inappropriate secretion of antidiuretic hormone.^[11]

Propranolol

Propranolol, a well-tolerated, non selective, B-adrenergic receptor blocker, has been commonly used so far for cardiologic indications in young children. In 2008, Leaute-Labreze et al, reported the incidental finding that propranolol can control the growth of IHs efficiently.^[12] Other studies done since then on this drug have shown an excellent effect and good tolerance.^[13] Within hours of starting therapy, propranolol produces vasoconstriction, resulting in a reduction in the color of the hemangioma. Its primary effect, however, appears to be alteration in the progression of angiogenesis in the hemangioma. Regulation of hemangioma growth involves basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). It is theorized that propranolol may decrease expression of bFGF and VEGF. Based on examination of hemangioma tissue, Truong and co-workers have also speculated that beta-adrenergic antagonists may ablate catecholamine receptor signalling, decreasing cyclic AMP and reducing levels of VEGF. In addition, propranolol may promote involution of hemangiomas by triggering apoptosis in endothelial cells.^[12,14]

Aims & Objectives:

There are no strict evidence based studies to guide the therapy. Moreover data regarding comparative efficacy of steroid and propranolol is inadequate and overall number of children studied, given the high incidence of hemangioma is also inadequate. There is no data available on comparison between effect of single drug (Propranolol) versus combination of two drugs (Propranolol + Prednisolone) on infantile hemangioma. This prospective randomized controlled study, seeks to compare the efficacy of 1-Propranolol,

2- Prednisolone alone, 3 – Propranolol with Prednisolone.

In infants below 8 months with cosmetically disfiguring or functionally deranging infantile hemangiomas.

To standardize the dose and assess safety profile of propranolol for the treatment of hemangioma.

Material and Methods:

This prospective randomized comparative study on the effect of oral medication in infantile cutaneous hemangioma was conducted in the Post Doctoral Departmental of Paediatric Surgery, Sardar Vallabhai Patel Post Graduate Institute of Pediatrics (S.V.P.P.G.I.P), S.C.B. Medical College and Hospital, Cuttack, in Odisha between September 2012 to December 2014.. Patients were divided into 3 groups: Group A received propranolol alone, Group B prednisolone alone and Group C received combination of both. 10 patients were included in each group. Random sequence was generated using a computer programme and was done in a 1:1:1 ratio.

Inclusion Criteria:

1. Problematic infantile hemangiomas
 - a. Potentially disfiguring hemangiomas in the face
 - b. Functionally threatening hemangiomas of the limbs, genitalia, natural orifice.
2. Age Group: 1 week to 8 months of either sex.
3. Multiple lesions

Exclusion Criteria:

1. Uncomplicated hemangiomas of trunk, extremities
2. Infants with heart disease, cardiac arrhythmia
3. Broncho-obstructive disease
4. Known hypoglycaemia
5. Diabetes mellitus
6. Hypertension

7. Hypotension
8. Liver failure
9. Visceral hemangioma
10. Prematurity

Treatment was initiated during, a short hospitalization of 48 hours. At inclusion, each lesion was evaluated clinically for size, colour and consistency. Lesions were categorized into superficial, mixed and deep according to the depth measured on USG. The maximum diameter in 2 axis perpendicular to each other was measured. The lesion was photographed with and without flash with a standard 10 megapixel digital camera. ECG evaluation was done to rule out treatment contraindications. In patients with eyelid involvement, ophthalmologic examinations were done. Clinical assessment with measurements and photographs was repeated at 24 and 48 hours of starting treatment.

The drug protocols used in the various groups:

Group A:

Propranolol was given at a starting dose of 1 mg/kg/per day. (in powdered form mixed with sweetening agent) in 2 divided doses and increased to 2 mg/kg/day on the second day, if tolerated well. In case of adequate response with only minor side effects, the drug was continued at 1 mg/kg/day. Maximum dose given to a patient was 2 mg/kg/day and was given only if the lesion did not improve further for more than 1 month at any point of treatment. In the absence of side effects, the child was discharged and treatment was continued at home for a minimum of 3 months.

Group B:

Commercially available liquid prednisolone was started at 1 mg/kg/day in two divided doses after feed for a period of 3 weeks. It was discontinued for 2 weeks and then restarted in a similar on/off fashion to reduce drug side effects. Maximum dose given to a patient in this group was 4 mg/kg/day. Minimum

duration of the treatment was 3 months. If response is not adequate the dose is increased by 1 mg/kg/day in each cycle.

Group C:

This group received combination of both the drugs as per above protocol for a minimum of 3 months. (i.e propranolol maximum 2 mg/kg/day in two divided doses and prednisolone, maximum 2 mg/kg/day in two divided doses) maximum dose of both drugs given to a patient was 2 mg/kg/day. Each in two divided doses per day.

After discharge all the children were reevaluated after 8 days of treatment and then every month for a minimum of 3 months. Doses were adjusted for weight increases every month of follow-up. Monthly evaluations consisted of clinical and photographic evaluations of the IH and monitoring of treatment compliance and tolerance (heart rate and blood pressure). For assessment of patients with eyelid involvement, ophthalmic examinations were repeated as needed. Although not a part of the study, treatment was continued till the age of 1 year unless complete resolution occurred. Therapy was tapered off over the last month and patients were continued on follow up to look for relapse.

Measure of assessment was based on Visual Analogue Scale (VAS) ranging from -10 to + 10 by comparing follow-up images to pre treatment baseline photograph. On the VAS, 0 represented the baseline photograph (Pre-treatment), a decrease in colour or size in a (-) number. VAS measurements of photographic documentation were available at time points 0(baseline), 1, 2days, 1 week, 1,3,6,12,18 months. Images were evaluated by 2 independent examiners blinded to the group to which the patient belongs.

The assessors scored the improvement into one of the following categories:

0-24%, 25-49%, 50-74% and 75-100%.

In case of major drug side effects, patients were withdrawn from the study. Treatment was considered complete when

- (a) Normal skin colour was achieved
- (b) VAS reduction >75% with residuum
- (c) No re-growth till 1 month of stopping treatment.

Primary outcome measure :

Proportion of patients in each group with at least 75% improvement in the extent of the hemangioma as compared prior to treatment based on

- a) Clinical evaluation (assessment of healing, change in consistency and geometric measurements)
- b) Change in VAS based on clinical photographs
- c) Parental satisfaction

Secondary outcome measures:

- a) Difference in extent/size versus colour changes in each group
- b) Adverse events during therapy in each group.
- c) To standardize the dose of propranolol.

Statistical Analysis

The statistical analysis was carried out using *Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows)*. All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of skewness and *Kolmogorov Smirnov* tests of normality. For normally distributed data means was compared using *student's t-test for groups*. For skewed data *Mann-Whitney test* was applied for group. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using *Chi square or Fisher's exact test* whichever was applicable. For time related variables *Repeated Measure ANOVA* was applied followed by *One-way ANOVA* for normally distributed data or *Wilcoxon Signed Rank test* for skewed data. All statistical tests

were two-sided and were performed at a significance level of $\alpha=0.05$.

Observation And Results

Patients and treatment

Thirty patients with IH were included in the study, with 10 patients randomly allocated to each group. Group A (n=10) received propranolol, Group B (n=10) received prednisolone and Group C (n=10) received both propranolol and prednisolone.

Gender:

Of the 30 infants, there were 18 boys and 12 girls (M:F=3:2). Specific ratio in each group was group A 2.1:1, group B 2:3 and group C 2.1:1.

All patients who received treatment were full term except for one patient in group B who was born preterm at 32 weeks of gestation at initiation of treatment patient was older than 2 months. At the time of initiation of treatment, no patient was on any concomitant therapy.

Age at initiation of treatment:

Mean age of initiation in group A was 4.6(1-8) months, in group B 5.5 (2-8) months and in group C was 4.7 (1-8) months.

Location:

Head and neck was the most common location of hemangioma accounting for 66% (n=20) of total patients of the study. Parotid was the most common site in head and neck region contributing 30% of total cases, followed by lip (13.3%) and scalp (10%).

Type:

Most common type of lesion was superficial - 16 (53%), followed by mixed-8 (26%) and deep-6 (20%). The ratio of superficial: deep: mixed was 7:2:1 in group A, 4:3:3 in group B and 5:3:2 in group C.

Symptomatology:

Most lesions were noticed by parents in second to fourth week of life as painless swellings which started proliferating rapidly.

Complicated hemangioma:

Group A, (n=1): ulceration with bleeding

Group B, (n=1): tongue hemangioma with feeding difficulty

Group C, (n=3): ulceration with bleeding (2), ulceration only(1)

Bleeding lesions were seen in the lip, labial and scapular region. A total of four (13.3%) patients presented with ulcerated lesions, one (3.3%) belonged to group A and three (10%) belonged to group C. Most parents were apprehensive because of rapid growth of lesion and fear of tumor/malignant potential.

Age at end of study:

Mean age (months± SD) at the end of study in group A was 15.3 ± 5.2, in group B was 18.1 ± 4.3 and group C was 15.8 ± 4.1. there was no statistical difference among the 3 groups.

Follow up duration:

Mean duration (months± SD) of follow up in group A was 10.6 ± 4.3, in group B was 13.11 ± 3.3 and group C was 10.4 ± 3.4. There was no statistical difference among the 3 groups.

Treatment completion:

Five patients completed treatment in group A at mean age of 12.8 (11.4-22.1) months and after a mean treatment duration of 9.9 (4-14.5) months. Five patients had ongoing therapy with propranolol at the end of study. In group B, four patients completed treatment at a mean age of 18.25 (12-25) months after mean treatment duration of 13.25 (8-19) months and in group C, only two patients could complete treatment by the end of study. Mean age at the end of treatment in group C was 16.5 (11-22) months after mean treatment duration of 9.5(3-16) months. There was no statistical difference in age at completion and treatment duration among three groups.

Response time:

All patients responded except for one in group B. Mean response time (days) in group A (4.1 ± 3.3 SD) and group C (4.7 ± 3.4 SD) was significantly

lower than in group B (9.78 ± 7.8 SD) [p<0.047]. The three sub-groups of infants with superficial (n=16), followed by deep (n=6) and mixed (n=8) were compared regarding their treatment response. The response time was significantly less in mixed type compared to superficial and deep [p<0.024].

Response measurements:

Response was measured on the basis of

- (a) Clinical evaluation including assessment of healing, two dimensional geometric measurements and assessment for change in consistency
- (b) VAS
- (c) Parental satisfaction.

Healing:

Group A – Ulceration was seen in 1(3.3%) patient as it was associated with bleeding. This was a large ulcerated, bleeding scapular hemangioma which was managed very effectively where bleeding stopped within 24 hours and ulcer healed within 3 months.

Group C – Ulceration was seen in 3(10%) patients and it was associated with bleeding in 2(66%). Two of these healed completely within one month and the third patient with infected forearm hemangioma required discontinuation of prednisolone and healed in 2 months with propranolol only.

There was no patient of ulcerated lesion in group B for comparison.

Geometric measurements : All lesions stopped growing with all three types of treatment. All lesions decreased in size in all three groups except one patient in group B. Maximum reduction was seen in group A in first three months of treatment with mean reduction of 35.5 ± 21.3%, followed by group C which showed a mean reduction of 31.7 ± 24.1%. Group B showed least reduction of three groups with a mean of 21.5 ± 21.7%. All lesions but one continued to decrease in size measured at 6 months,

12 months and 18 months but there was no statistically significant difference in two-dimensional reduction in size among three groups.

Change in consistency:

Significant change in consistency was noted within 24 hours in group A compared to group B and C which showed delayed change in consistency at 8 days of treatment.

Visual Analogue Scale:

The following parameters were studied using VAS.

(a) **Colour fading :** Significant colour fading was seen in group A in first 2 days of treatment compared to group B and C ($p=0.031$). VAS for colour fading reached +2 within 24 hours in group A whereas same VAS was reached in group B and C at 8 days of treatment. Thereafter all lesions except one in group B continued to fade significantly in colour compared to baseline in all three groups. After 3 months, fading of colour was reached with a VAS of +5 (+3 to +7) for group A, +4.5 (0 to +7) for group B and +5.5 (04 to +8) for group C. After 6 months fading of colour was reached with a VAS of +7(+5 to +9) for group A, +6 (0 to +8) for group B and +7(+5 to +9) for group C. After 12 months fading of colour was reached with VAS of +7.5(+6 to +9) for group A, +6.25(0 to +9) for group B and +8(+6 to +9) for group C. At end of study fading of colour was reached with a VAS of +9(+8 to +10) for group A, +8(0 to +9) for group B and +9(+7 to +10) for group C.

(b) Flattening:

Flattening of lesions was more and occurred significantly earlier in group A and C than group B($p<0.05$). VAS for flattening reached -2(0to-5) within 48 hours for both group A and C compared to -2(0to-4) seen in group B at 8 days. Flattening was equally seen in group A and C. There was no difference in flattening based on type of lesions.

(c) Reduction in size:

All IH stopped growing, faded in colour and became smaller except one patient in group B. Lesion reduction based on VAS was significantly more in Group A and C at 3,6,12, 18 months compared to group B. Mean reduction (%) \pm SD at 3 month for group A, B and C was 58.21 ± 19.50 , 36.57 ± 18.97 and 49.99 ± 19.25 respectively. At 6 months it was 71.21 ± 18.35 , 46.94 ± 26.839 and 71.07 ± 17.69 for group A, B and C respectively. At 12 months it was 85 ± 11.32 , 66.25 ± 31.20 and 79.18 ± 13.94 for group A,B and C respectively. At 18 months it was 89.88 ± 10.26 , 66.64 ± 32.36 and 82.64 ± 10.35 for group A,B and C respectively. In Group A and C significant improvement was seen in 3 months ($p=0.005$, $p=0.005$), 6 months ($p=0.005$, $p=0.008$), 12 months ($p=0.005$, $p=0.008$) and 18 months ($p=0.02$, $p=0.04$) compared to baseline whereas in group B significant improvement was seen only at 6 months ($p=0.008$) compared to baseline.

The three sub-groups of infants with superficial (n-16), mixed (n=8) and deep (n=6) were compared

Table 1 : VAS for colour fading at different time periods

Group	24 hrs	48 hrs	8 day	3 mons	6 mons	1 year	1.5 year
A	0 (-1to+1)	+2 (-1to+2)	+2.5 (+1to+3)	+5.0 (3to+7)	+7 (5to+9)	+7.5 (6to+9)	+9 (+8to+10)
B	-.13 (1to0)	.05 (-1to+1)	+2 (-1to+2)	+4.5 (0to+7)	+6 (0to+8)	+6.25 (0to9)	+8 (0to9)
C	.25 (0to1)	.75 (0to3)	+2 (+1to+5)	+5.5 (+4to+8)	+7 (+5to+9)	+8 (+6to+9)	+9 (+7to+10)

Table – II : Mean size reduction (%) ± SD at different time periods based on Visual Analogue Scale.

Group	3mo	6mo	1yr	1.5yr
A	58.21 ± 19.50 (p=0.005)	71.21 ± 18.35 (p=0.005)	85 ± 11.32 (p=0.005)	89.883 ± 10.2615 (p=0.002)
B	36.57 ± 18.974 (p=0.061)	46.94 ± 26.839 (p=0.008)	66.250 ± 31.2083 (p=0.072)	66.640 ± 32.36 (p=0.068)
C	49.99 ± 19.255 (p=0.005)	71.07 ± 17.694 (p=0.008)	79.189 ± 13.9457 (p=0.008)	82.640 ± 10.3587 (p=0.004)

regarding their treatment response. The changes of VAS did not differ significantly either for size or colour at any of the time points among these three groups.

There is significant fading of colour and decrease in size of the IH during the follow up period compared to the photographs at point 0 in group A and C whereas in group B, change in colour and size seen is very less at corresponding time periods.

Doses schedule and requirement:

All medications were started at the dose of 1 mg/kg/day in two divided doses. After observation for 24 hours dose was increased to 2 mg/kg/day in two divided doses in all three groups. In case of early response within 24 hours or more early side effects same dose was continued. Mean dose requirement at the end of the study in group A for propranolol was 1.8 ± 0.63 SD, for prednisolone in group B was 2.60 ± 0.79 SD, for prednisolone in group C was 1.9 ± 0.61 SD and propranolol in group C was 1.8 ± 0.63 SD. It was observed that mean dose requirement for prednisolone in group C was significantly lower than in Group B (p<0.003). It was also observed that one patient in group A and group C did not require any increase in dose and were managed at an initial dose of 1 mg/kg/day only. One patient in group B did not show any response till end of study inspite of receiving maximum dose at 4 mg/kg/day. There was no decrease in requirement of propranolol in group C inspite of adding prednisolone compared to group A. dose requirement in three types of hemangiomas did not differ significantly.

Side effects:

In group B and C, significantly higher numbers of complications were noted along with poor treatment compliance.

Group A:

There were two complications seen in group A, one patient of upper lip hemangioma had asymptomatic hypoglycaemia at start of propranolol treatment, which was managed with frequent feeding. Second patient had somnolence after second dose of propranolol at 1 mg/kg. There was no evidence of hypoglycaemia, bradycardia or hypotension in this patient as cause of somnolence. Dose was continued at 1 mg/kg/day in these two patients till 1 month of follow up. Second patient has completed his treatment while first patient is still on treatment at dose of 2 mg/kg/day with a lesion reduction of 87.5% till end of study. No patient required discontinuation of treatment for any reason. Patient compliance and parental satisfaction was 100%.

Group B :

In group B nine out of ten patients had one or more complications (p=0.017), most of which was Cushionoid appearance (n=5), followed by GI upset (n=3), re-growth at end of 3 week cycle of prednisolone (n=3). One patient did not show any response and had failure to thrive at 18 months of follow up (weight <5th centile). This child's birth weight was 1400 gm but weight at initiation of treatment at 4 months of age was 3.5kg. One patient

of forearm hemangioma had ulceration and infection requiring discontinuation of prednisolone and settled with oral and topical antibiotics.

Group C:

Seven out of ten had one or more complications ($p=0.039$), most of them were because of prednisolone and are Cushionoid ($n=6$), GI upset ($n=4$), re-growth ($n=1$) and infection ($n=1$).

Discussion :

Infantile hemangioma is the most common vascular tumor in infancy with an incidence of upto 10% in white infants. It occurs 2.5 to 4.1 times more frequently in females and in upto 20% in premature infants.^[15] In this study, males were more than female (3:2). This could be explained by the possibility of parental reluctance of providing health care to the female children in this part of the country. IHs most commonly occur in the head and neck region but may present anywhere in the skin, mucous membranes, or underlying viscera and can have both aesthetic and functional consequences.¹⁶ This is seen in the current study as well where head and neck have constituted 66% of total case.

Because most IHs remains uncomplicated and regress spontaneously without sequelae, no active therapy is routinely indicated. It is well documented the IHs that become complicated by ulceration, bleeding, or impingement on vital structures such as airways or eyes warrant active management.^[2,5] Although there are some reports that superficial ulcerated hemangioma can respond to various modalities but the gold standard treatment of complicated IHs for a long time has been the use high-dose corticosteroids.^[7,10] Since the report of Leaute- Labreze et al in 2008, propranolol has been widely used for the treatment of problematic hemangiomas, even though no randomized controlled trials have come out with their final analysis.

This study conducted randomized controlled prospective and tried to evaluate the efficacy and

safety of propranolol and prednisolone when used alone and in combination.

Ulceration is the most frequent complication, occurring in upto 15% of patients.^[17,18] It can lead to pain, irritability, poor feeding or sleeping, scarring and disfigurement.^[2,19] It is also associated with bleeding (41%) and infection (16%). In this study, ulceration was seen in 13.3% patients and it was associated with bleeding in 75% and infection in 25% cases. Although the exact mechanism is not fully understood, factors contributing to ulceration include surface friction and maceration.^[18] Once ulceration occurs, it is often challenging to manage but in this study one large ulcerated, bleeding scapular hemangioma was managed very effectively with propranolol alone where bleeding stopped within 24 hours and ulcer healed within 3 months. Remaining three patients of ulcerated hemangioma were receiving both propranolol and prednisone, two of which healed completely within a month and third with infected forearm hemangioma required discontinuation of prednisolone and healed in 2 months with propranolol only, this was comparable to the study conducted by San et al on 32 patients where painful ulcerations healed completely within 2 months with propranolol.^[20]

Use of systemic corticosteroids is limited to the proliferative phase, halting growth rather than producing significant involution.^[20,21,22] In addition, response rates vary widely, and many IHs fail to respond at all.^[6] In this study too, mean response time (days) in patients receiving prednisolone alone was significantly more (9.78 ± 7.8) ($p < 0.047$) than patients receiving propranolol alone or combination of both. Mean reduction of more than 25% at 1 month was only 10%. There was no added advantage of combining two drugs in term of response time. All patients responded in each group except for one patient in group B. The response time was significantly less in mixed type compared to superficial and deep lesions. ($p < 0.024$). This observation is in contradiction to study by Rossler J et al^[23] on 38 children with proliferating

hemangiomas treated with systemic corticosteroids at dose of 2 mg/kg/day as first-line treatment in 23(56%) and as second-line therapy after failure of laser and/or cryotherapy in 18 hemangioma (44%) where mean duration of therapy was 129.0 and 137.6 days in first and second-line corticosteroid therapy, respectively. Efficacy after 2 weeks of therapy, defined by a response of more than 25% shrinkage during treatment, was noted in 86% of hemangiomas treated with corticosteroids as first line therapy and in all hemangiomas treated as second-line therapy.

In a study conducted by Sans et al^[20] propranolol could be discontinued in 15 of the 32 cases, at ages ranging from 6 to 14 months (mean:9.4 months). It was administered for a mean total duration of 6.1 months. This is comparable to the present study where five patients completed treatment in group A at mean age of 12.8 (11.4-22.1) months and after a mean treatment duration of 9.9 (4-14.5) months. Mean response time was also less than half of prednisolone, i.e.4.1 days^[20].

Side effects of steroids are also a major consideration in their use. Rossler et al reported 215 complications during prednisone therapy^[23]. Behavioural changes like irritability or insomnia were observed in 25% patients, 8% slipped off their individual growth curve for height; however, all three had catch-up growth after termination of steroid therapy. A total of 5% developed mild arterial hypertension requiring antihypertensive therapy. Cushionoid facies was observed to various extents in all children, while gastric irritation with feeding problems or reflux symptoms was absent. Bacterial or fungal infections were not observed. It is found in this study that in group B out of ten patients (90%) had one or more complications, mostly Cushionoid appearance (50%) followed by GI upset (30%). In addition there was re growth at the end of each 3 week cycle in 30% cases. 10% had failure to thrive at 18 months of follow up (weight <5th centile). 10% had infection requiring discontinuation of prednisolone.

In group C, 70% patients and one or more complications, most of them were again because of prednisolone (Cushionoid 60%, GI upset 40%, re-growth 10% and infection 10%). It is important to note that the incidence of re-growth was less compared to group B, indicating the efficacy of the additional propranolol. In group A however, only 2 patients had minor asymptomatic complications which did not require any active management. This is in agreement with study by Schiestl et al where no patient experienced any worrisome side effects with propranolol at a dose of 2 mg/kg^[13].

Schiestl et al reported recurrence' in two of the 14 patients who completed treatment with propranolol. Mild re-growth and darkening of colour was noted 8 weeks after discontinuing therapy^[13]. These patients had been treated with propranolol at 2 mg/kg/day for a total of 11 and 8.5 months, and therapy was stopped at the age of 14.3 and 12.3 months, respectively. Both improved on re-starting propranolol. In this study, no recurrence was seen in group A. Five (50%) of the patients had complete resolution 6 to 15 months after starting medication, at which time they were 9 to 19 months old. Dose given ranged from 1 to 2 mg/kg/day in these patients. In group B, however 4 patients completed prednisolone therapy 8 to 19 months after starting medication at dose of 2 to 3 mg/kg/day. At this time they were 12 to 25 months old. One of these children had recurrence 1 month after stopping therapy. He was treated for scalp hemangioma for 12 months at 2 mg/kg/day and his age at the end of treatment was 18 months.

Thus effectiveness and side effect profile appears more favourable with propranolol compared to prednisolone alone or in combination and should replace therapy with steroids in the management of IH, especially complicated ones. Although this is a prospective randomized study the limitations of this study is acknowledged due to relatively small sample.

Conclusion

1. Propranolol administered orally at 2 mg/kg/day had a consistent, rapid therapeutic effect, leading to considerable shortening of the natural course of IHs compared to prednisolone.
2. Propranolol is safer, well tolerated and had minimal side-effects than prednisolone which was associated with considerable higher incidence of complications requiring frequent tapering and stoppage of drug.
3. Propranolol therapy is more cost-effective than oral corticosteroids in treating IHs.
4. Administration of oral propranolol is safe in infants less than eight weeks of age and cause rapid and desirable regression of lesions with minimal and manageable adverse effects.
5. Propranolol is highly effective in treating complicated hemangiomas where response was seen as short as 24 hours.
6. Combination of propranolol and prednisolone had comparable efficacy to propranolol alone but was associated with higher number of complications, thereby decreasing patient compliance.
7. Recurrence of IH may occur if propranolol is withdrawn after a relatively short course of treatment (less than 6 months) and/or tailed off rapidly.

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What is already known? Prednisolone (oral) and propranolol are used as drug of choice in IH.

What is study adds – Propranolol is of better efficacy and without much side effects in treatment of IH.

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