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Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: A randomized controlled study

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Abstract

Aims and Objectives: The purpose of this study was to compare the efficacy of orally administered propranolol versus prednisolone versus both in the treatment of potentially disfiguring or functionally threatening infantile hemangiomas.

Material and Methods: A prospective study of 30 patients aged 1 week–8 months was randomized into three equal groups. These were as follows: A, propranolol (2–3 mg/kg/d); B, prednisolone (1–4 mg/kg/d); and C, receiving both for a minimum duration of 3 months. Dimensions, color, consistency, ultrasonography, photographic documentation based on Visual Analogue Scale (VAS) were recorded before and periodically after starting treatment. A minimum 75% improvement was considered as success with no regrowth up to 1 month of stopping treatment.

Results: Mean initial response time (days) in A (4.1 ± 3.3 SD) and C (4.7 ± 3.4SD) was significantly lower than B (9.78 ± 7.8SD) ($p < 0.047$). Significant change in consistency was noted very early in A (24 hours) compared to B and C (8 days). VAS results are as follows: (a) color fading—significant reduction in A within 48 hours compared to B and C ($p = 0.025$), (b) flattening—more significant and earlier in A and C than B ($p < 0.05$), and (c) mean reduction in size: significant in A and C at 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 ($p = 0.02$, $p = 0.04$), whereas in B, it was seen only at 6 months ($p = 0.008$).

Conclusions: Propranolol had a consistent, rapid therapeutic effect compared to prednisolone. A combination of the two had a comparable but not higher efficacy than propranolol alone. Prednisolone was associated with a higher number of complications, thereby decreasing patient compliance.

Infantile hemangiomas (IHs) are the most common soft-tissue tumors of infancy, occurring in 4% to 10% of children under 1 year of age [1]. Within the first weeks of life, they enter a phase of rapid growth lasting for 3 to 6 months which may go on for 24 months. A period of stabilization for a few months follows with spontaneous involution usually occurring in several years. Regression is complete in 60% of 4-year-olds and 76% of 7-year-old patients [2]. Owing to this benign, self-limited course, therapeutic abstention is the rule.

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However, 10% require treatment during the proliferative phase, because of life-threatening location, local complications, or cosmetic/functional risks [3]. These include oral corticosteroid therapy as first-line treatment and interferon or vincristine as second- or third-line therapeutic agents. Since 2008, use of propranolol has come to the forefront because of its efficacy and minimal side effects [4]. There are no strict evidence-based studies to guide therapy. There is paucity of data comparing efficacy of steroid and propranolol and the effect of a single drug (steroid) versus combination of two drugs (steroid plus propranolol). In this prospective, randomized, controlled study, we compared the efficacy of propranolol alone, prednisolone alone vs combination of the two in infants below 8 months with cosmetically disfiguring or functionally deranging IHs.

1. Material and methods

Thirty patients with IHs attending the outpatient department of a tertiary referral hospital from January 2011 to July 2012 complying with the following criteria were included in the study: age group—1 week to 8 months of either sex and problematic IHs with potentially disfiguring lesions in the face or functionally threatening lesions of the limbs, genitalia or natural orifices. The following were excluded: uncomplicated lesions of trunk, extremities; presence of heart disease, cardiac arrhythmia; bronchoobstructive disease; history of hypoglycemia; diabetes mellitus; hypertension; hypotension; liver failure; visceral lesions and prematurity

Patients were divided into three groups: Group A received propranolol alone, Group B received prednisolone alone and Group C received a combination of both. Ten patients were included in each group. Random sequence was generated using a computer program in a 1:1:1 ratio.

Prior approval was taken from the Institute's Research and Ethics Committee (IRB reference no. MS/1615/M.Ch/5005).

Treatment was initiated during a short hospitalization of 48 hours. At inclusion, each lesion was evaluated clinically for size, color, and consistency. Lesions were categorized into superficial, mixed and deep according to the depth measured on ultrasonography (USG). The maximum diameter in two axes perpendicular to each other was measured. The lesion was photographed with and without flash with a standard 5-megapixel digital camera at 30-cm distance and approximately 2-Mb resolution. Electrocardiographic (ECG) evaluation was done to rule out treatment contraindications. In patients with eyelid involvement, ophthalmologic examination was done. Clinical assessment with measurements and photographs was repeated at 24 and 48 hours of starting treatment.

The drug protocols used in the three groups were as follows:

Group A: Propranolol was prepared by the hospital pharmacy as sachets containing a homogeneous mixture of propranolol and mannitol. It was given at a starting dose of 1 mg/kg per day, in two divided doses and increased to 2 mg/kg/d 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/d. Maximum dose was kept at 3 mg/kg/d and was given only if the lesion did not improve further for more than 1 month at any point of treatment. Blood pressure, heart rate and blood glucose were monitored 1 hour after the first dose and 4 hourly thereafter during the first 24 hours of treatment and then at 48 hours. In the absence of side effects, the child was discharged and treatment was continued at home.

Group B: Commercially available liquid prednisolone was started at 1 mg/kg/d in two divided doses after feed for a period of 3 weeks. As per current department policy, it was discontinued for 3 weeks and then restarted in a similar on/off fashion to reduce drug side effects. Maximum dose was kept at 4 mg/kg/d.

Group C: This group received a combination of both the drugs as per above protocol.

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 increase in weight. Monthly evaluation consisted of clinical and photographic evaluations of the IHs and monitoring of treatment compliance and tolerance (heart rate and blood pressure). Ophthalmological examinations were repeated as needed in patients with eyelid involvement. 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. In case of major drug side effects, patients were withdrawn from the study.

Measure of assessment for color and size was based on Visual Analogue Scale (VAS) ranging from −10 to +10 by comparing follow-up images to the baseline photograph pretreatment. Here, 0 represented the baseline photograph, a decrease resulting in a minus number and an increase in a + number. Measurements were available at time points 0, 1 day, 2 days, 1 week, 1 months, 3 months, 6 months, 12 months and 18 months. The images were evaluated by two independent blinded examiners who scored the improvement as: 0–24%, 25%–49%, 50%–74% and 75%–100%.

Treatment was considered complete when (a) normal skin color was achieved, (b) VAS reduction was >75% with residuum and (c) there was no regrowth until 1 month of stopping treatment.

Primary outcome measures are as follows:

Proportion of patients in each group with at least 75% improvement in the extent of the IHs 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 are as follows:

(a) Difference in extent/size versus color changes in each group.

(b) Adverse events during therapy in each group.
(c) Standardization of the dose of propranolol.

1.1. Statistical analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows) was used. 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 were 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 $\alpha = .05$.

2. Results

The overall male/female ratio was 3:2. (A 2.1:1, B 2:3 and C 2.1:1). No patient was on any concomitant therapy at the time of initiation of treatment.

Mean age of initiation of treatment was 4.6 months (1–8) in group A, 5.5 months (2–8) in group B and 4.7 (1–8) months in group C. Head and neck were the most common locations in 66% ($n = 20$). Parotid was the most common site in head and neck region contributing 30% of total cases, followed by lip (13.3%) and scalp (10%). The most common type of lesion was superficial (16; 53%), followed by mixed (8; 26.7%) and deep (6; 20%). The superficial/deep/mixed ratio was 7:2:1 in group A, 4:3:3 in group B and 5:3:2 in group C. Most lesions were noticed by parents in second to fourth weeks of life as painless swellings which started proliferating rapidly.

Complicated hemangiomas were seen in 5: group A, ulceration with bleeding (1); group B, tongue hemangioma with feeding difficulty (1); and group C, ulceration with bleeding (2) and ulceration only (1). Bleeding lesions were seen in the lip, labial and scapular region.

Mean age (months ± SD) at the end of the study was 15.3 ± 5.2 (group A), 18.1 ± 4.3 (group B) and 15.8 ± 4.1 (group C). Mean duration (months) of follow-up was 10.6 ± 4.3 (group A), 13.11 ± 3.3 (group B) and 10.4 ± 3.4 (group C). There was no statistical difference among the three groups.

Five patients completed treatment (as per definition) in group A at a mean age of 12.8 (11.4–22.1) months and a mean treatment duration of 9.9 (4–14.5) months. 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 completed treatment at the end of the study at a mean age of 16.5 (11–22) months and a mean treatment duration of 9.5 (3–16) months. There was no statistical difference among the three groups.

All patients responded to therapy except one in group B. Mean response time (days) in group A (4.1 ± 3.3 SD) and group C (4.7 ± 3.4SD) was significantly lower than that in group B (9.78 ± 7.8 SD) ($p < 0.047$). The response time was significantly less in mixed type compared to superficial and deep ($p < 0.024$).

2.1. Healing of ulceration

For group A, in a large ulcerated, bleeding scapular hemangioma, bleeding stopped within 24 hours and ulcer healed within 3 months. For group C, ulceration was seen in three (10%) patients and it was associated with bleeding in two. Two of the three ulcerated lesions healed completely within 1 month while the third with infected forearm hemangioma required discontinuation of prednisolone. There was no patient with ulcerated lesion in group B for comparison.

All IHs stopped growing, faded in color and became smaller except one in group B.

2.1.1. Geometric measurements

Maximum reduction was seen in group A in the first 3 months of treatment with a mean reduction of 35.5% ± 21.3%, followed by group C with a mean reduction of 31.7% ± 30.3%. Group B showed the least reduction with a mean of 21.5% ± 21.7%. All lesions except one in group B continued to decrease in size at 6, 12 and 18 months but there was no statistically significant difference in two-dimensional reduction in size among the three groups.

2.1.2. Change in consistency

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

2.2. VAS

2.2.1. Color fading

Significant color fading was seen in group A in the first 2 days of treatment compared to group B and C ($p = 0.025$) (Fig. 1). VAS reached −2 within 48 hours in group A whereas the same was reached in groups B and C at 8 days of treatment. Thereafter all lesions except one in group B continued to fade significantly in color compared to baseline (Table 1).

2.2.2. Flattening

VAS reached −2 (0 to −5) within 48 hours for both groups A and C compared to −2 (0 to −4) in group B at 8 days ($p < 0.05$). Flattening was equally seen in groups A and C. There was no difference in flattening based on the type of lesion.

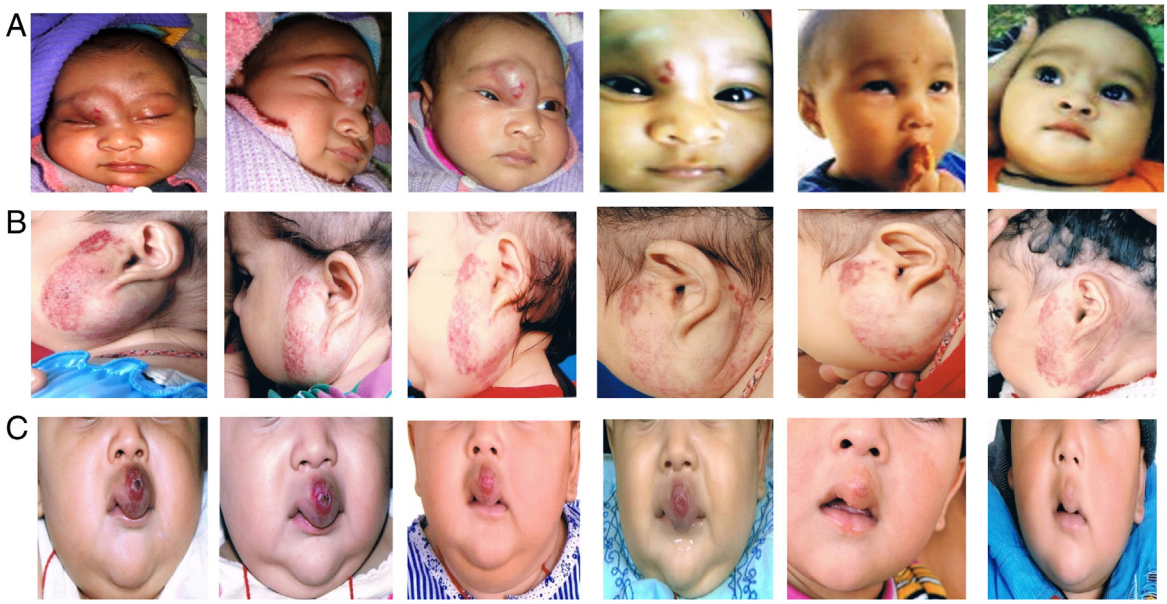

Fig. 1 Clinical photographs of patients in groups A, B and C showing change in color and size of the lesion at admission, 1, 3, 6, 9 and 12 months of treatment (from left to right).

2.2.3. Reduction

Reduction was significantly more in groups A and C at 3, 6, 12 and 18 months compared to group B (Table 2). In groups A and C significant improvement was seen at 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 ($p = 0.02$, $p = 0.04$) whereas in group B significant improvement was seen only at 6 months ($p = 0.008$) compared to baseline.

The above changes in VAS did not differ significantly at any of the time points between superficial, mixed and deep lesions.

The mean dose requirement (mg) at the end of the study was as follows: propranolol (group A) 2.25 ± 0.78 SD, prednisolone (group B) 2.60 ± 0.79SD, propranolol (group C) 2.2 ± 0.63SD and prednisolone (group C) 1.6 ± 0.51SD. The mean dose requirement for prednisolone in group C was significantly lower than that in group B ($p < 0.003$). One patient each in group A and group C did not require any increase in dose and was managed at the initial dose of 1 mg/kg/d. One patient in group B did not show any response till the end of the study in spite of receiving a maximum dose at 4 mg/k/d. There was no decrease in requirement of propranolol in group C in spite of adding prednisolone. Dose requirement in the three types of IHs was not statistically significant.

2.2.4. Complications

Significantly higher numbers of complications were noted along with poor treatment compliance in groups B and C.

2.2.5. Group A

There were two complications; one patient with upper lip hemangioma had asymptomatic hypoglycemia at the start of treatment, which was managed with frequent feeding. The second had somnolence after the second dose of propranolol at 0.5 mg/kg with no evidence of hypoglycemia, bradycardia or hypotension. The drug was continued at 1 mg/kg/d in these two patients. No patient required discontinuation of treatment for any reason. Patient compliance and parental satisfaction were 100%.

2.2.6. Group B

Nine patients had one or more complications ($p = 0.017$): Cushingoid appearance ($n = 5$), gastrointestinal (GI) upset ($n = 3$) and regrowth at the 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 g but weight at initiation of treatment at 4 months of age was 3.5 kg. One patient with forearm hemangioma had ulceration and infection requiring discontinuation of prednisolone and settled with oral and topical antibiotics.

2.2.7. Group C

Seven had one or more complications ($p = 0.039$), mostly caused by prednisolone: Cushingoid appearance ($n = 6$), GI upset ($n = 4$), regrowth ($n = 1$) and infection ($n = 1$).

3. Discussion

Hemangiomas are benign growths of endothelial cells presenting anywhere in the skin, mucous membranes, or underlying viscera. They most commonly occur in the head and neck region as seen in our study also where they

Table 1 Color fading ± SD at different time periods based on Visual Analogue Scale.

Group	24 hr	48 hr	8 d	3 mo	6 mo	1 yr	1.5 yr
A	0 ± 0.7 ($p = 0.07$)	−2 ± 0.9 ($p = 0.025$)	−2.5 ± 0.90 ($p = 0.007$)	−5.0 ± 1.1 ($p = 0.007$)	−7 ± 1.1 ($p = 0.011$)	−7.5 ± 1.5 ($p = 0.012$)	−9 ± 1.7 ($p = 0.009$)
B	−0.13 ± 0.35 ($p = 1.000$)	−0.05 ±0.53 ($p = 0.317$)	−2 ± 0.64 ($p = 0.011$)	−4.5 ± 2.3 ($p = 0.018$)	−6 ± 2.6 ($p = 0.018$)	−6.25 ± 2.7 ($p = 0.019$)	−8 ± 2.9 ($p = 0.021$)
C	0.25 ± 0.46 ($p = 0.16$)	0.75 ± 1.1 ($p = 0.109$)	−2 ± 1.3 ($p = 0.011$)	−5.5 ± 1.4 ($p = 0.011$)	−7 ± 1.4 ($p = 0.011$)	−8 ± 1.5 ($p = 0.012$)	−9 ± 1.5 ($p = 0.011$)

accounted for 66% of the cases [5]. There were more males than females (3:2) in our study as compared to the literature where it is quoted to occur 2.2 to 4.5 times more often in females [1].

Up to 10% of IHs may cause obstruction of the upper airway/eye, ulceration, bleeding, soft-tissue deformity, and high-output heart failure [6]. The gold standard treatment of complicated IHs for a long time has been high-dose systemic corticosteroids. They have been shown to be antiangiogenic in a number of in vitro settings [7]. In addition, they may influence capillary vascular tone. Their use is limited to the proliferative phase, halting growth rather than producing significant involution [8]. Even at a dose of 2–5 mg/kg per day, response rates range from 30% to 60%, mostly seen as stabilization or incomplete regression [9,10]. While their efficacy is not disputed, complications are frequent [11,12]. Boon et al. [6] noted Cushingoid facies (71%), personality changes (21%), gastric irritation (21%), fungal infection (6%) and reversible myopathy (one patient) in 62 patients receiving systemic steroid therapy for problematic IHs. While most complications are transient and limited, some may become much more serious, such as hypertension and hypertrophic obstructive cardiomyopathy. Rössler et al. [13] noted behavioral changes like irritability/insomnia (25%), poor height gain (8%) and hypertension (5%) during prednisone therapy. Cushingoid facies was observed to various extents in all children, although they had catch-up growth after termination of therapy with no gastric irritation or infections. In our study, prednisolone treatment led to Cushingoid appearance in 50% followed by GI upset (30%) in group B. In addition, there was regrowth at the end of each 3-week cycle in 30% cases. Failure to thrive at 18 months of follow-up (weight <5th centile) and infection requiring discontinuation of prednisolone were seen in 10% each. In group C, 70% patients had one or more complications, most of them again caused by prednisolone namely Cushingoid features (60%), GI upset (40%), regrowth (10%) and infection (10%). While most complications regress with discontinuation of therapy, they cause a lot of anguish to parents or require withholding therapy for a while.

Propranolol, a well-tolerated, nonselective, ß-adrenergic receptor blocker had been commonly used for cardiologic indications in young children. In 2008, Léauté-Labréze et al. [4] reported the incidental finding that it could control the growth of IHs efficiently. Other studies done since then have shown an excellent effect and good tolerance [14]. Within hours of starting therapy, it produces vasoconstriction, resulting in a reduction in the color of the hemangioma. Its primary effect appears to be alteration in the progression of angiogenesis, perhaps by decreasing expression of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [4]. It may ablate catecholamine receptor signaling, decreasing cyclic AMP promoting involution by triggering apoptosis in endothelial cells [4,15].

Response rates to steroid therapy vary widely with many IHs failing to respond at all [9]. In our study, mean response

Table 2 Mean size reduction (%) ± SD at different time periods based on Visual Analogue Scale.

Group	3 mo	6 mo	1 yr	1.5 yr
A	58.2 ± 19.5 ($p = 0.005$)	71.2 ± 18.4 ($p = 0.005$)	85 ± 11.3 ($p = 0.005$)	89.8 ± 10.3 ($p = 0.02$)
B	36.6 ± 18.9 ($p = 0.061$)	46.9 ± 26.8 ($p = 0.008$)	66.3 ± 31.2 ($p = 0.072$)	66.6 ± 41.6 ($p = 0.068$)
C	49.9 ± 19.2 ($p = 0.005$)	71.1 ± 17.7 ($p = 0.008$)	79.2 ± 13.9 ($p = 0.008$)	82.6 ± 10.4 ($p = 0.04$)

time in patients receiving prednisolone alone was 9.78 ± 7.8 days, which was significantly more ($p < 0.047$) than patients receiving propranolol alone or combination of both. Mean reduction in size of more than 25% at 1 month was only 10% in group B. There was no added advantage of combining two drugs in terms of response time. Rössler et al. [13] treated proliferating IHs with systemic corticosteroids at a dose of 2 mg/kg/d as first-line treatment in 23 (56%) and as second-line therapy after failure of laser and/or cryotherapy in 18 (44%). Mean duration of therapy was 129.0 and 137.6 days respectively. Efficacy after 2 weeks of therapy, defined as more than 25% shrinkage, was noted in 86% in the first group and in all given as second-line therapy. In another study, propranolol could be discontinued in 15 of the 32 cases, at ages ranging from 6 to 14 months (mean 9.4 months) [16]. It was administered for a mean total duration of 6.1 months. This is comparable to our study where five patients completed treatment in group A at a 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 (days) with propranolol was also less than half of prednisolone, that is, 4.1 vs 9.78 ($p < 0.047$).

Qin et al. [17] treated 58 children with propranolol (dose 1.0– 1.5 mg/kg/d). The outcome was excellent in 17.2%, good in 60.4%, moderate in 20.7% and poor in 1.7% of cases. Buckmiller et al. [18,19] evaluated 32 patients treated with propranolol (dose 2 mg/kg/d) by clinical examination (treating physicians) and assessment of photographs by blinded physicians, revealing 50% of patients to be excellent responders, 47% partial responders and 3% nonresponders. Minor adverse effects included somnolence in 27% of patients, gastroesophageal reflux in 9%, respiratory syncytial virus exacerbation or rash in 4.5%. Bagazgoitia et al. [15] in a retrospective study treated 71 patients of IHs with propranolol (dose 2 mg/kg). At 20 weeks, the average reduction was 60% but after that less impressive size reduction was obtained. In our series, significant color fading, flattening and reduction in size were seen in group A compared to the other two groups. Only two had minor asymptomatic complications which did not require any active management. Schiestl et al. [14] also had a similar experience where no patient experienced any worrisome side effects with propranolol at a dose of 2 mg/kg. Five patients (50%) had complete resolution 6 to 15 months after starting medication, at which time they were 9 to 19 months old.

The most frequent complication of IHs is ulceration occurring in up to 15% of patients and is a challenge to manage [20,21]. It can lead to pain, irritability, poor feeding or sleeping, scarring, and disfigurement [22,23]. It is also associated with bleeding (41%) and infection (16%) [23]. Contributory factors include surface friction and maceration [21]. In our study, ulceration was seen in 4 (13.3%) patients with bleeding in 75% and infection in 25%. A large scapular hemangioma treated with propranolol alone showed stoppage of bleeding within 24 hours and healing of ulcer within 3 months. The rest received a combination of propranolol and prednisone as per randomization. Two of these healed completely within a month. Another infected forearm hemangioma required discontinuation of prednisolone and healed in 2 months with propranolol only. This was comparable to the study conducted by Sans et al. [16] on 32 patients where painful ulcerations healed completely within 2 months of propranolol therapy. Two other small series of ulcerated IH have shown early and good response to oral propranolol at a dose of 1–2 mg/kg per day with no side effects [24,25].

Schiestl et al. [14] reported recurrence in 2 of the 14 patients who completed treatment with propranolol at 2 mg/kg/d for a total of 11 and 8.5 months. Therapy was stopped at the age of 14.3 and 12.5 months, respectively. Mild regrowth and darkening of color were noted 8 weeks after discontinuing therapy. Both improved on restarting propranolol. In our study, no recurrence was seen in group A.

Data regarding comparative efficacy of steroid and propranolol and effect of single versus combination of two drugs are inadequate in spite of the high incidence of IHs. Manunza et al. [26] reported use of propranolol in 30 IHs. The average age at the start of therapy was 5.8 months (range 1.2–13.5 months) initiated at a dose of 1 mg/kg/d increased to 2 mg/kg/d after 1 week. Nine were treated after failure to respond to corticosteroids. Two were treated with both prednisolone and propranolol, while the rest received only propranolol. Nineteen infants successfully completed treatment and the remaining demonstrated significant improvement. The majority responded within a week of initiating propranolol. No significant adverse effects were reported. Truong et al. [27] reported an infant with a subglottic and mediastinal hemangioma who having failed previous attempts at surgical resection was put on a combination of oral propranolol (2 mg/kg/d) and prednisolone (3 mg/kg/d). The patient's stridor resolved within 2 days of starting drug treatment. An MRI performed a week later revealed a 50% reduction in size. Prednisolone was tapered off at that time, while the propranolol was continued for 5 months. It was tapered off with no recurrence of symptoms. In our study, in group C, there was regrowth in only 10% compared to 30%

in group B, indicating the efficacy of the addition of propranolol. Price et al. [28] compared the use of propranolol with corticosteroids in 110 patients with IHs. They found that 82% of patients in the propranolol group improved by 75% or more, compared with 29% of patients in the steroid group. One patient on propranolol had hypoglycemia, but all patients in the steroid group had at least one adverse event. The propranolol therapy was about half the cost of steroid therapy. They concluded that propranolol should be considered a first-line therapy for IHs.

Effectiveness and side effect profile appear more favorable with propranolol compared to prednisolone alone or in combination and should replace therapy with steroids in the management of IHs, especially complicated ones. Although we did a prospective randomized study we acknowledge the limitations of our study. The relatively small sample size of our groups because of time constraint of study period limits the inferences that can be applied to the clinical situation. Therefore, to confirm and elevate the reliability of the present results, more extensive clinical studies and inclusion of more complicated and visceral hemangiomas are required. This will help us understand in more detail the efficacy and safety of propranolol alone and prednisolone alone vs combination of the two in infants with cosmetically disfiguring or functionally deranging hemangiomas.

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