Original Article

To compare intralesional and oral propranolol for treating periorbital and eyelid capillary hemangiomas

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Purpose: A pilot randomized control trial to compare the efficacy and side effects of intralesional and oral propranolol in periorbital and eyelid capillary hemangiomas. **Methods:** Twenty patients were prospectively randomized to two groups of ten each. Group 1 was initiated on oral propranolol 1 mg/kg/day titrated to final dose of 3 mg/kg/day over 1 week which was continued for 6 months and then tapered over 1 week; Group 2 received 3 doses of direct intralesional propranolol hydrochloride 1 mg/ml; 0.2 ml/cm 4–6 weeks apart. Hemangioma area and corneal astigmatism were measured. **Results:** Within each group at 6 months there was a significant reduction in area (group 1: 83.48 ± 11.67%, P = 0.0019; group 2: 67.78 ± 21.71%, P = 0.0019) and improvement in astigmatism (pre, post: group 1: 2.98D @ 179.8°, 1.13D @ 179.8°, P = 0.0045; group 2: 1.62D @ 90.16°, 0.75D @ 179.9°, P = 0.0001). There was no difference in area reduction (P = 0.056), change in appearance (P = 0.085), ptosis (P = 0.23) and side effects (lethargy, poor feeding; P = 0.171) between the two groups. **Conclusion:** Efficacy and side effects with intralesional propranolol are comparable to oral propranolol for periorbital and eyelid lesions.

Key words: Capillary hemangioma, intralesional propranolol, oral propranolol

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Capillary hemangiomas, now known as infantile hemangiomas, are common benign tumors of infants with a prevalence of 0.1 to 0.28% in the Indian population.[1] Most periorbital lesions are observed as the regression rate is 30% by age three and 70% by age seven.[2,3] However, in the presence of associated ophthalmic complications like mechanical ptosis, astigmatism, amblyopia (anisometropic or deprivational), disfiguring proptosis, exposure keratopathy, optic nerve compression, lesion necrosis or infection, intervention is required.[4-6]

Oral propranolol hydrochloride obtained FDA approval in March 2014 as a first line therapy.[7] The proposed mechanisms of action for beta blockers include vasoconstriction, suppression of angiogensis and induction of apoptosis of the endothelial cells.[8-11] Though rare, systemic side effects can be associated with oral propranolol.[12-14]

Awadein *et al*. documented a statistically comparable response without any side effects with intralesional propranolol and intralesional triamcinolone in periocular hemangiomas.[15] The rationale for intralesional propranolol is direct drug delivery with possible additional beneficial effect of the injection procedure. We planned to evaluate intralesional propranolol as an alternative to oral and compare the efficacy and safety profile.

Methods

The study protocol was approved from institutional ethics committee and was registered with the Clinical Trials Registry of India (CTRI/2017/08/009440). The study and data collection were compliant with the principles of the Declaration of Helsinki.

Twenty consecutive patients with periorbital and eyelid capillary hemangioma attending the oculoplasty clinic were assigned to two groups after block randomization using a computer-generated random number table. Patients having posterior intraconal spread of lesion, ulceration or necrosis, previously treated lesions, or patients with a history of systemic illnesses and a failure to obtain cardiology clearance for intervention were excluded. Informed consent was taken from the parent or guardian including consent for photographic documentation and permission to use them for publishing.

At baseline, a detailed clinical history and systemic evaluation was done. The body weight was recorded at baseline and all subsequent follow ups. The size, location, color, type, and appearance of lesion, associated complications like ptosis, strabismus, fixation preference were documented. Cross sectional flat surface area was calculated with the help

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of digital calipers (length along longest linear dimension (LLD) and width perpendicular to the LLD, Fig. 1).

Visual acuity was recorded whenever possible using an age appropriate method with Teller Acuity Cards and Cardiff Acuity Cards, monocularly. The corneal astigamtism was recorded using a handheld auto refractometer (Retinomax 3+ (Rmax); Nikon Inc., Japan). Imaging was done using orbital ultrasonography and magnetic resonance imaging (MRI) in all patients. Abdominal ultrasonography, when indicated, was done to document any visceral hemangiomas. Photographs of the lesions were taken at baseline and on monthly follow ups. The final evaluation was done at 6 months.

Study groups

1. Group 1: Ten patients received oral propranolol in a dose of 1 mg/kg/day in two divided doses on day 1 and 2; 2 mg/kg/day on day 3 and 4 followed by 3 mg/kg/day continued till 6 months. Dose was modified according to body weight at each follow up when required. At 6 months, the dose was tapered off over a period of 6 days.

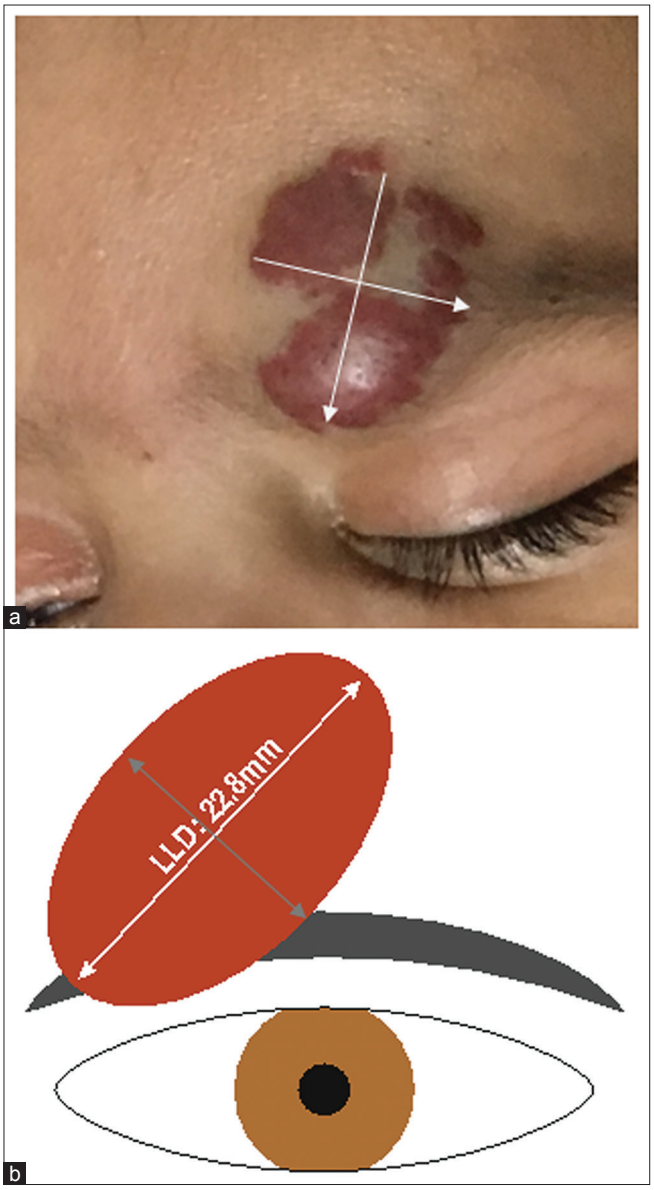

Figure 1: (a) Clinical photograph of a case with a brow lesion; (b) Diagrammatic representation of the same case for measuring the longest linear dimension (LLD) and cross sectional area

2. Group 2: Ten patients received intralesional propranolol hydrochloride (1 mg/ml formulation provided by the hospital pharmacy) in a dose of 0.2 ml per cm of the LLD with a maximum dose of 1 ml. Direct intralesional injection was administered using a 1 ml syringe with a 26-gauge needle. Number of injection sites varied from one to four depending upon size of lesion. The injections were administered under general anesthesia with cardiorespiratory monitoring. All patients received three injections at day 0, between 4 to 6 weeks, and between 8 to 12 weeks.

Efficacy of therapy was measured as regression in size on clinical examination. The percentage decrease in cross sectional area was noted. This was further categorized into a scale as excellent (≥90%), very good (70 to 89.9%), good (50–69.9%), fair (30–49.9%), and poor (<30%); modified and adapted from Awadein *et al*.[15] Other efficacy parameters included change in color, appearance, improvement in ptosis and change in corneal astigmatism. The change in color and appearance was assessed using subjective scales, designed and ratified by independent observers before the study. The representative images of the scales are depicted in the results. Amount of ptosis was measured as the difference in mm of the upper lid margin to central corneal reflex distance in mm (margin reflex distance, MRD1) of both eyes. This was categorized into none, mild (<2 mm), moderate (2–4 mm), and severe (>4 mm).

The keratometry was done with the help of a handheld auto kerato-refractometer and the amount of corneal astigmatism was noted as diffencre of dioptric keratometric power along K1 and K2 meridian along with the axis. The change in astigmatism after treatment in each group was compared as vectors.[16] This was done by calculating the mean preoperative and postoperative centroids, as described by Holladay *et al*.[17]

Systemic side effects like cold extremities, change in feeding habits, constipation, gastric reflux or regurgitation, history of jitteriness or lethargy, wheezing, bradycardia or hypoglycaemia. Local side effects like necrosis or ulceration at lesion site were documented. Any other side effects as reported by guardians or noted on evaluation during follow up were also noted. Data were recorded in a predesigned proforma and excel spreadsheet. Categorical variables were summarized as frequencies. Quantitative variables were summarized as mean ± SD or median if non-normally distributed. Quantitative data results were compared and interpreted using the two-sided students *t* test with an alpha error of 5% and a power of 80%. A *P* value of ≤0.05 was considered statistically significant.

Results

Baseline characteristics

Twenty patients were divided into 2 groups: group 1 (oral propranolol, case 1 to 10) and group 2 (intralesional propranolol, case 11 to 20). The baseline characteristics were statistically comparable except for gender. These are summarized in Table 1.

Type of lesion

The lesions were classified at baseline into four main types: skin surface localized, skin surface extensive, conjunctival surface localized, and deep orbital lesions [Fig. 2]. Majority had deep extensive lesions and the most common location was the upper lid. Three patients had associated cutaneous lesions outside the head and neck region. None of the patients showed any visceral lesions.

Outcome

a. Change in cross sectional area: All 10 patients in the group 1 showed significant response with an average reduction of 83.48% ± 11.67% at the end of 6 months (*P* value 0.0019). A similar response of 67.78% ± 21.71% was seen in all 10 patients in group 2 (*P* value 0.0019). This was statistically comparable in both groups (*P* value 0.056). The response was graded as excellent to poor. All 10 patients (100%) in group 1 had more than 65% improvement in area and the response was good or higher. As compared to this, only 80% of the patients in group 2 had a good or higher response. The mean area at baseline and six months are summarized in Table 2
b. Astigmatism: Both groups showed a significant reduction in mean dioptres of astigmatism. In group 1, at baseline, the mean cylinder was 2.86D at 179.8° which reduced to 1.13D at 179.8°. In group 2, the mean cylinder changed from 2.62D at 90.2° at baseline to 0.75D at 179.9° at the end of 6 months. This improvement was comparable between both groups (*P* value 0.49)
c. Change in color: The lesions were categorized on a subjective scale as dark red-blue, red, pink and same as surrounding skin, representative images of which are given in Fig. 3. In group 1, 70% had a dark red-blue color at baseline. At the end of 6 months, 80% had color same as surrounding structure. In group 2, 70% patients had a dark red-blue color at baseline. At the end of 6 months, only 30% patients had a color that was same as the surrounding skin. The overall improvement in color was better in group 1
d. Change in Appearance: The lesions were categorized into 4 types (significantly elevated, moderate, reduced, and flat) at baseline and at 6 months. As this was a subjective parameter recorded on clinical evaluation, representative images are given in Fig. 4. At baseline, 70% patients in group 1 had lesions that were significantly elevated. Three patients had mild elevation and were graded as grade 1. At the end of 6 months, all patients' lesions showed reduction in elevation with 60% patients having

Table 1: Summary of baseline characteristics in groups 1 and 2

Demographics	Group 1	Group 2	*P*
Age (median, mean+SD)	8 months, 8.2+3.7 months	10 months, 18.4+18.7 months	0.107
Gender	7 female, 3 male	2 female, 8 male	0.02
Cross Sectional Area	615.77±592.67 mm^2	332.3±261.94 mm^2	0.205
Type of lesion			0.475
Skin surface localized	1	4	
Skin surface extensive	1	1	
Conjunctival localized	3	2	
Deep orbital (extensive)	5	3	
Colour			0.549
Dark red-blue	7	7	
Red	2	3	
Pink	1	0	
Same as surrounding skin	0	0	
Appearance			0.08
Elevated	7	9	
Mildly elevated	3	1	
Flat	0	0	
Ptosis			0.98
None	4	2	
Mild <2mm	0	1	
Moderate 2-4mm	4	4	
Severe >4mm	2	3	
Astigmatism	2.8588 D at 179.8o	1.617 D at 90.16o	0.502

Table 2: Change in area of lesion from baseline to 6 months in groups 1 and 2

	Group 1 *n*=10		Group 2 *n*=10
Size of lesion (area) at baseline (mean±SD)	615.77±592.67 mm^2		332.3±261.94 mm^2
Size of lesion (area) at 6 months (mean±SD)	130.34±162.86 mm^2		132.89±149.76 mm^2
Average percentage area reduction (mean±SD)	83.48%±11.67		67.78%±21.71
P	0.0019		0.0019
P group 1 vs. group 2		0.056 (t-test)	

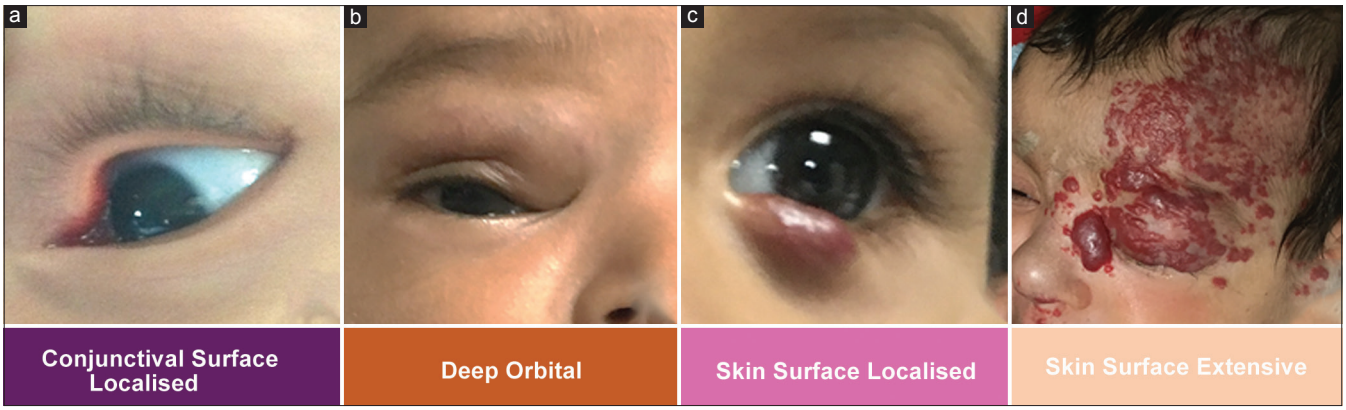

Figure 2: Representative images for clinical type of lesion: (a) conjunctival surface localized; (b) deep orbital; (c) skin surface localized; and (d) skin surface extensive

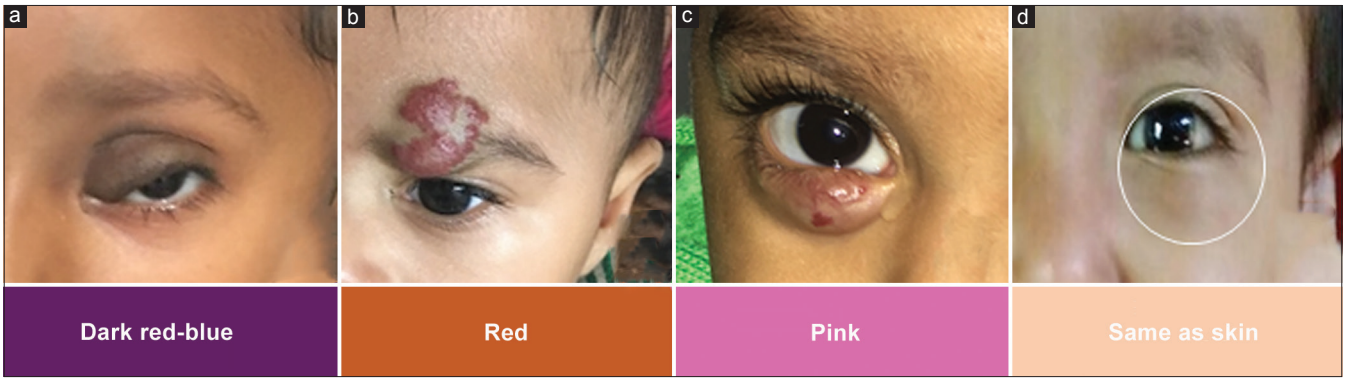

Figure 3: Representative images for color categories: (a) dark-red blue; (b) red; (c) pink; and (d) same as surrounding structure (skin)

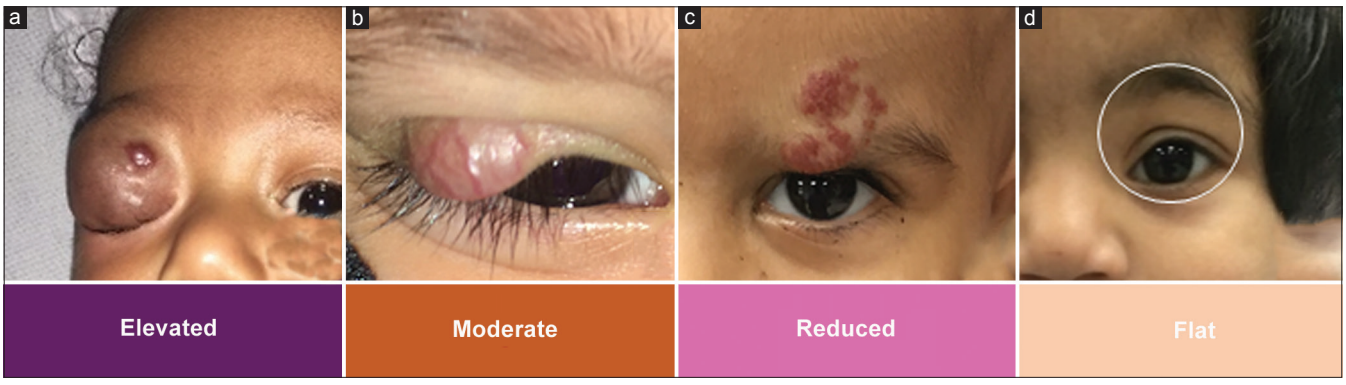

Figure 4: Representative images for appearance categories: (a) Markedly elevated; (b) Moderately elevated; (c) reduced; and (d) flat

flat appearance. In group 2, at baseline 90% had elevated and one patient had mildly elevated appearance. At the end of 6 months, 30% patients still had a significantly elevated lesion, and another 50% showed some reduction. Only 20% patients had a flat lesion

e. Change in Ptosis: There was improvement in ptosis in both the groups from baseline to 6 months. percentage reduction in ptosis was 66.11 ± 14.21% in group 1 (n = 6). In group 2, the average percentage reduction in ptosis was 45.91 ± 36.52% (n = 8). Two cases did not show any improvement in ptosis

f. Side effects of treatment: In group 1 (oral propranolol) 70% patients didn't report any side effects. Two patients developed lethargy and one reported poor feeding during the initial 6 weeks of oral propranolol. The parents were asked to monitor the children more frequently and administer the evening dose closer to bedtime. The dose was not reduced in the group and the treatment was continued as per protocol. None of the patients in group 2 (intralesional propranolol) reported any side effects

g. Retrospective subgroup analysis within group 2: Within group 2 receiving intralesional propranolol, we retrospectively compared the baseline characteristics of the five patients having excellent or very good response (>70%) with the remaining five patients and noted that these lesions had a smaller size at baseline (P value: 0.049).

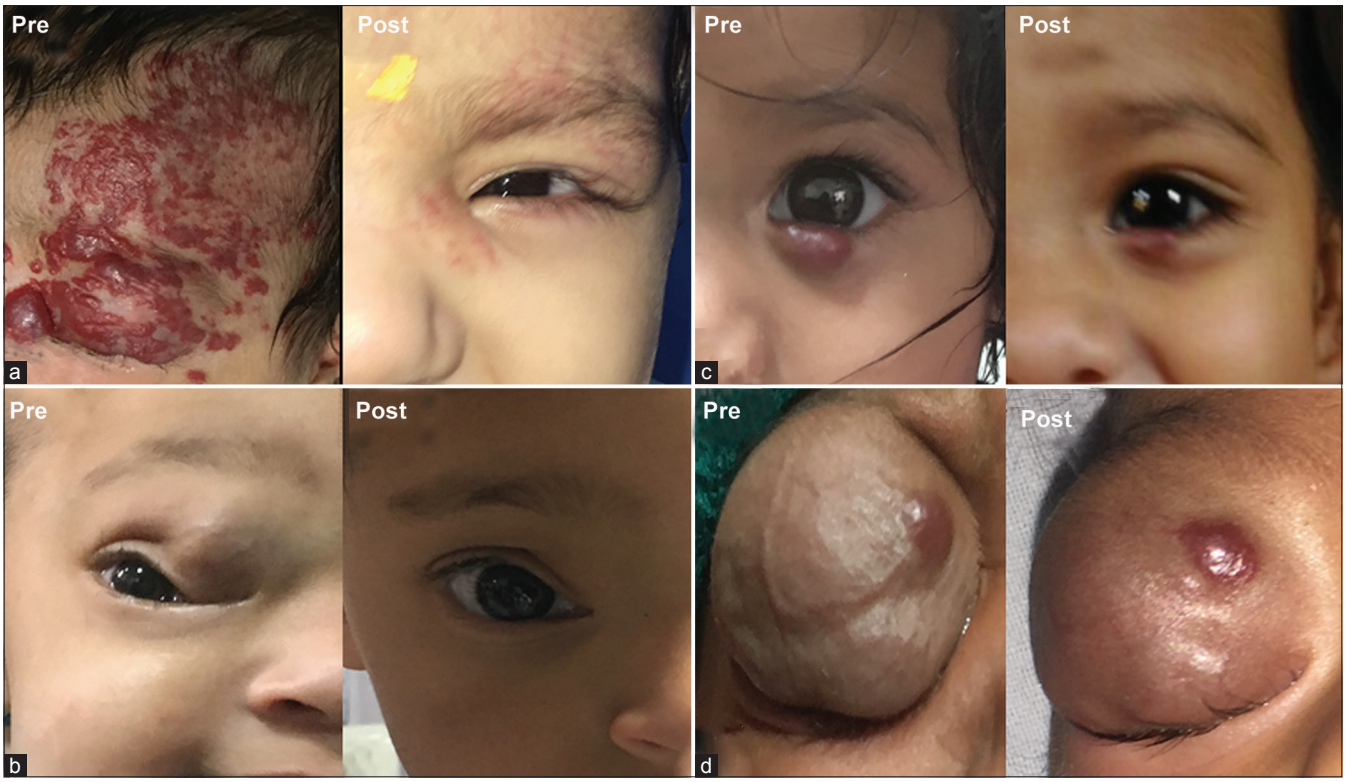

Figure 5: Case summaries pre (baseline) and post (6 months) treatment: (a) Case 4 - excellent response with oral propranolol; (b) Case 1 - good response with oral propranolol; (c) Case 15 - excellent response with intralesional propranolol; and (d) Case 11 - fair response with intralesional propranolol

The best and least response cases of each group are summarized in Fig. 5.

Discussion

Capillary hemangiomas are usually noted at birth, exhibit rapid postnatal growth followed by slow involution, often leading to a complete regression. Probable risk factors include female gender, prematurity, low birth-weight, placental anomalies, and multiple pregnancies.[18,19] In the present study, majority of the patients were male. The findings of low birth weight (n = 1), history of preterm delivery (n = 3) and twinning (n = 2) were seen in some patients in the present study. However, in the absence of a control cohort, we are unable to comment on the causative significance.

Hemangiomas can be classified as superficial, deep, or compound. The superficial lesions include red nodules without a subcutaneous component. A deep hemangioma protrudes with an overlying bluish tint or telangiectasia. Compound hemangiomas have both components. In the present study, we classified the periorbital lesions into skin surface localized, skin surface extensive, conjunctival surface localized and deep orbital lesions with majority patients having deep extensive lesions. Multifocal hemangiomas also exist, and infants with greater than five lesions should undergo workup to rule out visceral involvement.[20] In our study, three patients had associated cutaneous lesions outside the head and neck region. None of the twenty patients in the present study showed any visceral lesions.

Response to treatment

Oral propranolol is highly efficacious in cutaneous infantile hemangiomas with a reported response rate of 98% (range 82–100%).[12] Various studies have also reported a high efficacy of oral propranolol in periorbital hemangiomas.[21-27] In this study, a high efficacy was reported as reduction in area, improvement in color, and appearance of the lesions.

Awadein *et al*. compared intralesional steroid with intralesional propranolol injection in periocular capillary hemangiomas at 4 months and regression was noted in 10 out of 12 patients with intralesional propranolol.[15] Zaher *et al*. compared oral, topical, and intralesional propranolol for problematic cutaneous hemangiomas. An excellent response (complete resolution) was achieved in 60% patients with oral propranolol, in 20% with topical propranolol and only in 13.3% with intralesional propranolol. As intralesional application did not offer any benefit over topical and oral, it could not be recommended.[28] Torres-Pradilla *et al*. studied the role of intralesional propranolol in six patients with facial capillary hemangiomas. After the first injection, the patients were followed up at 4 weekly intervals and the injection was only repeated if there was response in the lesion. They concluded that overall beneficial role of intralesional propranolol in infantile hemangiomas was guarded.[29]

In the present study, at 6 months, there was a significant reduction in area of the lesions associated with improvement in color and appearance with intralesional propranolol. These results are significantly better than those reported previously.

On comparing the reduction in percentage area between groups 1 and 2 in the present study, there was no statistically significant difference (P value 0.056). Thus, in our study, even though the trend with oral propranolol was better, intralesional

propranolol was comparable to oral propranolol therapy at the 6-month analysis.

Associated complications

A study done by Haik *et al*. reported that complications could occur in up to 80% of untreated or treatment-resistant periocular capillary hemangiomas.[30] Anisometropia induced amblyopia affects up to 60% of these patients.[5,30,31] A study by Snir *et al*. reported the association of anisometropic astigmatism, refractive amblyopia and ptosis—induced amblyopia in periocular hemangiomas. They reported a reduction of 40.5% in mean cylindrical power at seven months with oral propranolol in 30 patients.[26] In the present study, keratometry was recorded in all patients and where possible, visual acuity was also documented. Both groups showed a significant reduction in astigmatism with treatment. However, a direct correlation of induced astigmatism with improvement in ptosis was not established and this was an independent response parameter.

Regression in size of lesion results in improvement of associated ptosis specifically with upper eyelid lesions. Harikrishna *et al*. have reported reduction in ptosis with oral propranolol in four patients.[32] In the present study, average percentage reduction in ptosis was better in group 1 than group 2 and was as a result in reduction in overall size of the lesion.

Side effects of therapy

Various studies have reported side effects of oral propranolol for capillary hemangiomas.[22-27,32-34] Systemic propranolol causes hypoglycemia, the early sympathetic signs of which are masked by beta blockers. Marqueling *et al*. reported the most common adverse events as sleep disturbances and acrocyanosis.[12] In a review on oral propranolol by Cornish *et al*., adverse effects were documented in 26 of the 100 cases.[35] In the present study, in group 1 two patients reported lethargy and one patient reported poor feeding. The parents were asked to monitor the child more frequently, administer the evening dose closer to bedtime and continue the treatment as per protocol.

The most serious and feared complication of orbital intralesional steroid injections is central retinal artery occlusion (CRAO).[36] Bang *et al*. recommended that while administering intralesional corticosteroid, retinal vessels should be examined during and after injection. Increased force while injecting or digital pressure after the procedure may cause retrograde flow of the drug particles into the central retinal artery.[37] Though this has been documented with steroid injection which is particulate in nature, propranolol being a solution may have a lower but potential risk for this complication.

In the present study, none of the ten patients in group 2 (intralesional propranolol) reported any side effects, local or systemic. All the injections were administered under general anesthesia with cardiorespiratory monitoring. Though none of the patients reported any side effects, it is pertinent to highlight the need for and potential side effects of general anesthesia for the procedure. Older children may be cooperative under topical anesthesia. Alternatively, the procedure may be undertaken under sedation with peri-operative analgesia. This may add to the logistics of the procedure.

Limitations

The small sample size and short duration of follow up are the major limitations of the present study. The response seen in the present study in both groups was attributed to the treatment intervention. It could have however occurred as a part of the natural course of the regression of the hemangioma. The median age in the present study was eight months (range 3–12 months, mean ± SD: 8.2 ± 3.7 months) in group 1 and 10 months (range 5–60 months, mean ± SD: 18.4 ± 18.7 months) in group 2. Thus, majority of the lesions were in the proliferating phase. However, in the absence of a control observation—only group we cannot conclude this finding and cannot attribute the results to intervention alone. The exposure of general anesthesia for the intralesional group poses an added disadvantage. Moreover, given the pediatric age group, in this single observer study with both objective and subjective response parameters, the accuracy of results can be validated with the help of photographs and meticulous documentation of records. This study had a final observation time point at 6 months of treatment. A longer follow up after cessation of treatment is required to assess any differences in rebound growth in the two groups.

Conclusion

To summarize, in contrast to two studies published by Zaher *et al*. and Torres-Pradilla *et al*., in the present study we found a statistically comparable response at 6 months with intralesional propranolol as compared to oral propranolol even though the outcome trend with oral propranolol was better. Within the group receiving intralesional propranolol, we retrospectively compared the baseline characteristics of the patients having excellent or very good response with the remaining patients who showed a lesser response. The lesions which showed a greater response had a smaller size at baseline. Thus, small, localized lesions showed significant response to intralesional propranolol.

Studies to analyze local concentration of drug after intralesional administration and detailed histopathological analysis to assess effect of injection procedure on the lesion can help better delineate the mode of action of intralesional propranolol. In addition, development of a depot formulation of propranolol for intralesional administration may help in improving its efficacy.

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Conflicts of interest

There are no conflicts of interest.

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