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RESEARCH ARTICLE

TIMOLOL IN CAPILLARY HEMANGIOMA IN INFANT

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Abstract

Background: The purpose of this study was to evaluate the effect of topical timolol in the management of periocular capillary hemangioma.
Objective: Efficacy of Timolol in Capillary Hemangioma
Methods: A prospective study was performed in 48 consecutive patients with periocularhemangioma. 24 patients underwent topical timolol and Next 24 patientreceived lubricating eye drops topical as a control group.The size of the lesion was measured serially every week during the first month, every 2 weeks for the second month, and then monthly for another 4 months. Therefractive statusand degree of ptosis if present were measured before and at the end of the study.
Results: There was reduction in the size of hemangioma, astigmatic error, and degree of ptosisin both the groups. The difference in outcome between two groups was statistically significant. Rebound growth occurred in 22.22% of the group Using timolol and 37.51% of the control group. No adverse effects were reported during or after topical timolol.
Conclusion: Topical timolol may have good efficacy fortreatment of infantile periocular hemangioma.

Introduction:-

Capillary hemangioma is the most common benign vascular eyelid tumor in childhood[1].This tumor has been referred by many names (infantile hemangioma, juvenilehemangioma,hemangioblastoma, benign hemangioendothelioma, hypertrophic hemangioma), but is mostcommonlycalled ‘capillary hemangioma.’ This term is most common as it accurately describes the capillary unit structure of endothelial cells surrounded by pericytes. [1,2]

It is present in 1%–4% of all births[2]and is more common in premature infants and often following chorionic villus sampling.[3]It is usually a cutaneous, subcutaneous, or deep orbital lesion and commonly presents a few weeks after birth.

It is present in up to 5% of all births. There is a 3:1 ratio of females to males. The incidence of orbit and eyelid hemangiomas is 1/10 that of systemic hemangiomas, which occurs in 10% of all children by 1 year of age. [15]

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The usual clinical course of infantile cutaneous or subcutaneous hemangiomas includes an initial engorgement (age 6–12 months) followed by regression (age 1–7 years). It usually regresses spontaneously and hence is kept under close observation. Active intervention is performed only if the lesion is very extensive and causes amblyopia, mechanical ptosis, exposure keratopathy, or optic neuropathy.

Treatment modalities for cutaneous or subcutaneous hemangiomas include topical[4] and oral beta blockers,[5,6,7,8] local and oral steroids,[9,10] surgical excision, immunotherapy,[11] laser photocoagulation with pulsed dye laser,[3] and embolization.[12]

Oral propranolol was also recently reported to be in use in the treatment of a case of bilateral sessile infantile hemangioma of posterior lamella of upper lid by Syed Ali Raza Rizvi et al., with clearing of visual axis within 12 weeks of treatment.

We selected this study because there is no any definite treatment for capillary hemangioma in infant and it occur in 10% of all children by 1 year of age so our main objective of this study is to find out the efficacy of Timolol in capillary hemangioma in infant.

We have selected this study under the guidance of senior most oculoplasty surgeon and Approval was obtained from the local ethics committee." from N.H.L.Municipal medical college, Ahmedabad for the year of 2011-12. There are no financial conflicts of interest to disclose."I will be responsible towards the co investigators for this project.

Many capillary hemangiomas can be diagnosed on examination, ultrasonography, computed tomography,magnetic resonance imaging for accurate diagnosis.

Understanding of this tumor, its natural history, and the indications for treatment are necessary for management of the tumor and to help the patient's family understand the disease process.

In the periorbital infantile hemangioma, treatment is usually expectant, unless vision is threatened. Interventions in the pastincluded sclerosing agent, surgical excision, cryopexy, diathermy was used. And now a day we are using oral or intralesional steroids, ά-interferon, vincristine, cyclophosphamide, lasers, embolization or surgical excision. Although these treatment modalities have their place, there are risks in usingsteroids and other pharmacological agents in young children. Surgery and other interventions also have risks. There have been recent reports of the successful use of propranolol as a relatively safe modality of treatment.

Aims and Objectives:-

Aim:-

To find out the effectiveness of Timolol in infantile capillary hemangioma

Objectives:-

1. To evaluate the effectiveness and safety of the topical timolol
2. To evaluate the astigmatic error in periocular hemangioma

Materials and Methodology:-

1. The study protocol was approved by the hospital ethics committee. The parent or guardian of each study patient gave their written informed consent.
2. This prospective study was performed in patients with periocular hemangiomas requiring intervention. The main indications for intervention included visual-threatening capillary hemangioma, or rapidly progressive or recurrently bleeding hemangioma. Vision-threatening hemangiomas were defined as hemangiomas causing obstruction of the visual axis or inducing astigmatism, strabismus, amblyopia, or anisometropia.

Prior to inclusion, all patients were subjected to a detailedcardiac evaluation, including history-taking, detailed clinicalexamination, and a 12-lead electrocardiogram, includingcalculation of heart rate, voltages, and intervals

Inclusion Criteria:

1. Infant aged less than 12 months

2. Infant with one or more hemangiomas of any sized
3. Infant not threatening for vital or functional structure and for which no treatment would be proposed
4. Informed consent
5. Patient with social insurance.

Exclusion Criteria:
1. Alarming hemangioma (s) (complicated forms or localization at risk)
2. Cardiac pathology (cardiac malformation, heart failure, cardiac arrhythmias, pulmonary hypertension)
3. Asthma
4. Bronchopulmonary dysplasia
5. Bronchiolitis
6. Raynaud's syndrome
7. Pheochromocytoma
8. Development of serious form of hemangioma (bleeding,necrosis, ulceration, infection, respiratory distress) requiring standard treatment

Study Group:
Group T: Timolol 0.5 % eye drop
Group C: Carboxymethyl cellulose0.5%

Study type:
Interventional

Study Design :
Prospective Randomized

Condition :
Infantile capillary Hemangioma

Enrollment :
48

Study Period:
May 2011 to December 2016

Method of administering drugs:
1. The first 24 patients received a Timolol 0.5% eye drops twice a day. The next 24 patients received carboxymethyl cellulose eye drops as placebo to control group.
2. All patientsunder Topical timololhad monitor with cardiovascular and respiratory monitoring for at least first 48 hours.
3. In addition, a dilated fundus examination was done with careful examination of the central retinal artery. Patients who underwent topical timolol were discharged after 48 hours of observation.

Follow-up:
1. Patients were followed up on a weekly basis for the first month, then every 2 weeks in the second month, and finally at 4-weekly intervals for a period of 4 months after the therapy.
2. The patients were followed up by an investigator blinded to the carboxymethylcellulose and topically treated.
3. The size of the hemangioma was measured by clinical examination and documented by serial photography. The area was then calculated in mm^2 and measured serially.
4. The response to therapy was graded as excellent, good, fair, or poor, according to the finaloutcome achieved at the time treatment was stopped (Table 1). Patients with rebound growth after resolution were documented.

In addition, cycloplegic refraction was performed for all patients before initiation of therapy and at the end of the study.

The degree of ptosis was assessed by comparing the maximum palpebral fissure height on both sides before the therapy and at the end of the follow-up period.

Table 1:- Grading system used in evaluation of Topical Timolol for treatment of periocular hemangiomas.

Excellent	Complete resolution achieved
Good	Sustained plateau, with >50% reduction in size of hemangioma
Fair	Sustained plateau, with <50% reduction in size of hemangioma
Poor	No response or worsening of hemangioma

Table 1

Observation and Result:-

A Total 48 patients of Capillary Hemangioma were examined on the basis of above mentionedcriteria's

Age wise distribution of Patients

Figure 1 shows the age wise distribution of patients in which **52.09%** of patients were between age of 9 to 12 month and **6.25 %** of patients were less than 2 months of age

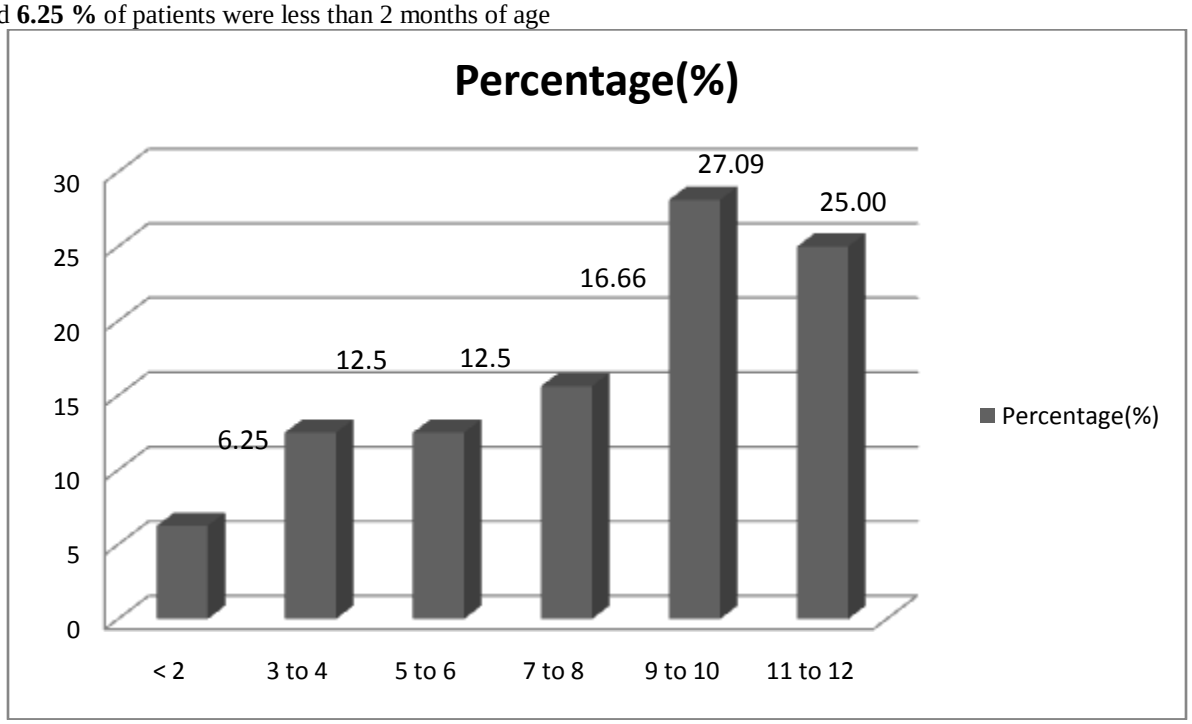

Figure 1:- Change in Size of Hemangioma after treatment.

Table 2:-

	Group T	**Group C**
Mean Size before treatment	10.50 +/- 3.21	19.66 +/- 4.53
Mean size after 3 months of treatment	4.13 +/- 2.03	11.06 +/- 5.53
T test	5.081 (P < 0.05),	4.710 (P < 0.05)

Table 2 show the mean size of capillary hemangioma before and after the treatment. Both the group shows significant improvement in size of capillary hemangioma after the treatment according to unpaired t test

Sex wise distribution of Pateints

Our study shows most Common sex were Female (75.00%) and male were (25%)

Site Of Capillary hemangioma in infant

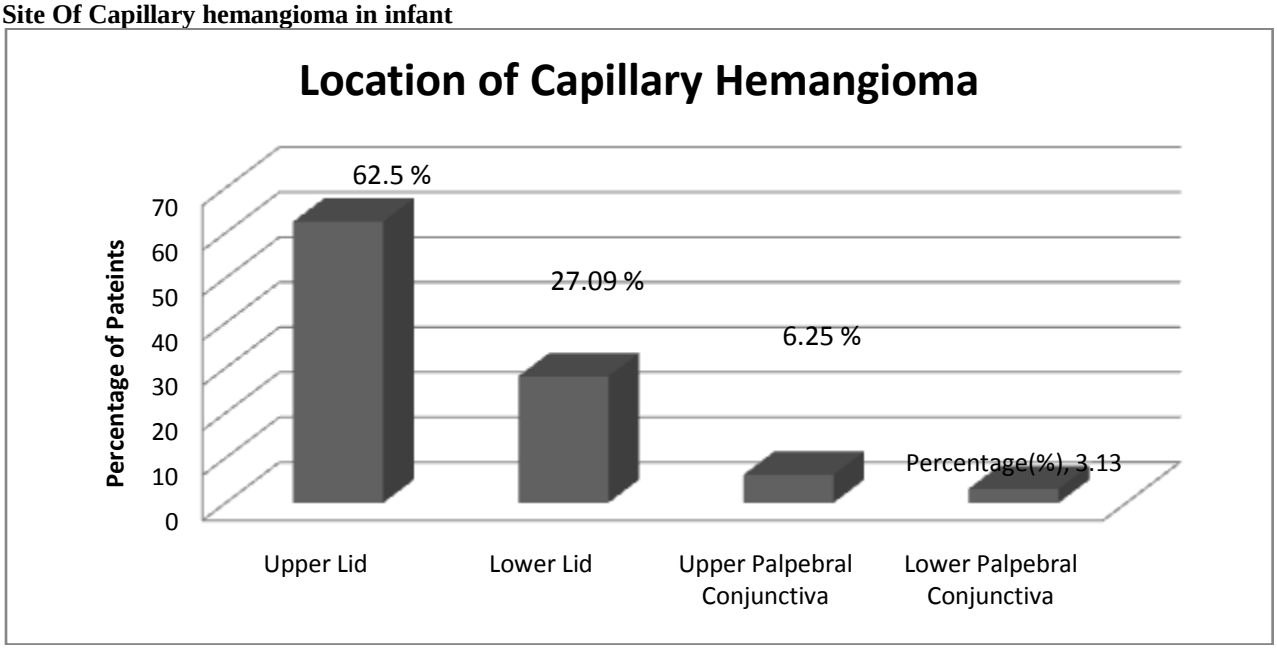

Figure 2:-

Figure 2 shows most common site for Capillary Hemangioma was Upper Lid (62.50%) , and less commonest(4.16%) lower palpebral conjunctiva.

Indication for Treatment

Figure 3 shows maximum no of patients 50.00% were treated for cosmetic reason.

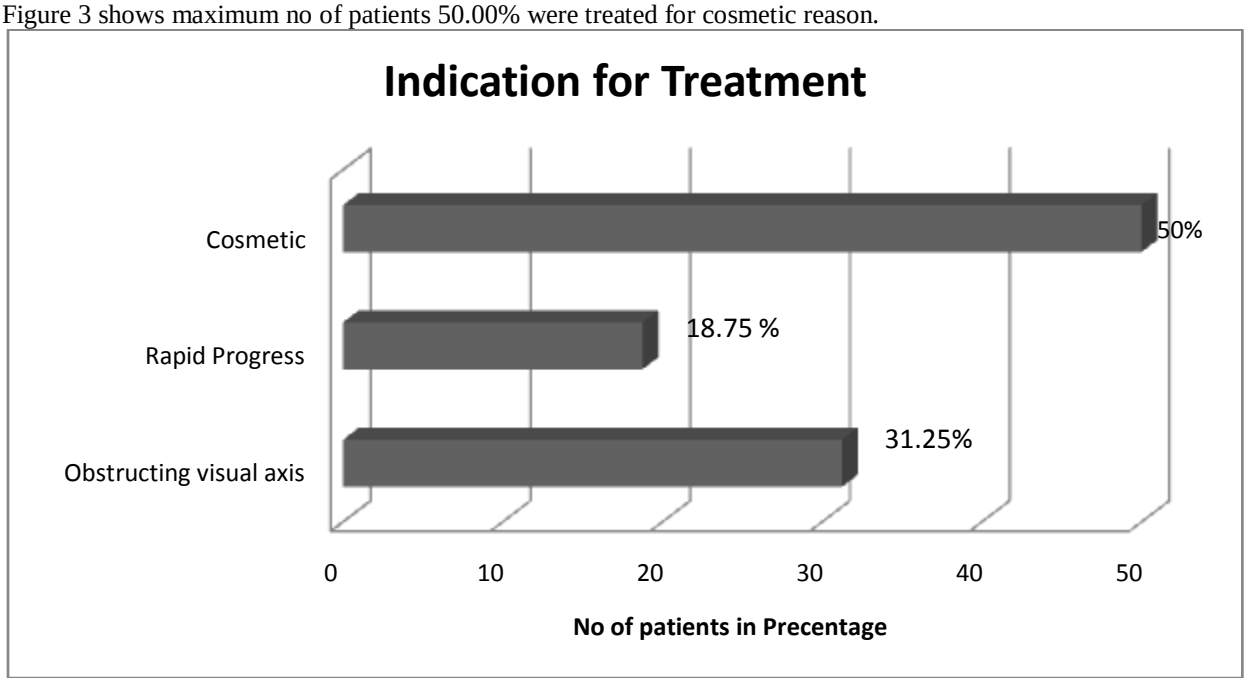

Figure 3

Type of Treatment

Our study shows the 50% of patients were undergone Topical Timolol and 50 % were undergone placebo(Carboxymethylcellulose) therapy as control group.

Response to Treatment

Figure 4 shows the response of patients to the treatment in which 75% of patient in Group T were show good and 58.33% in group C

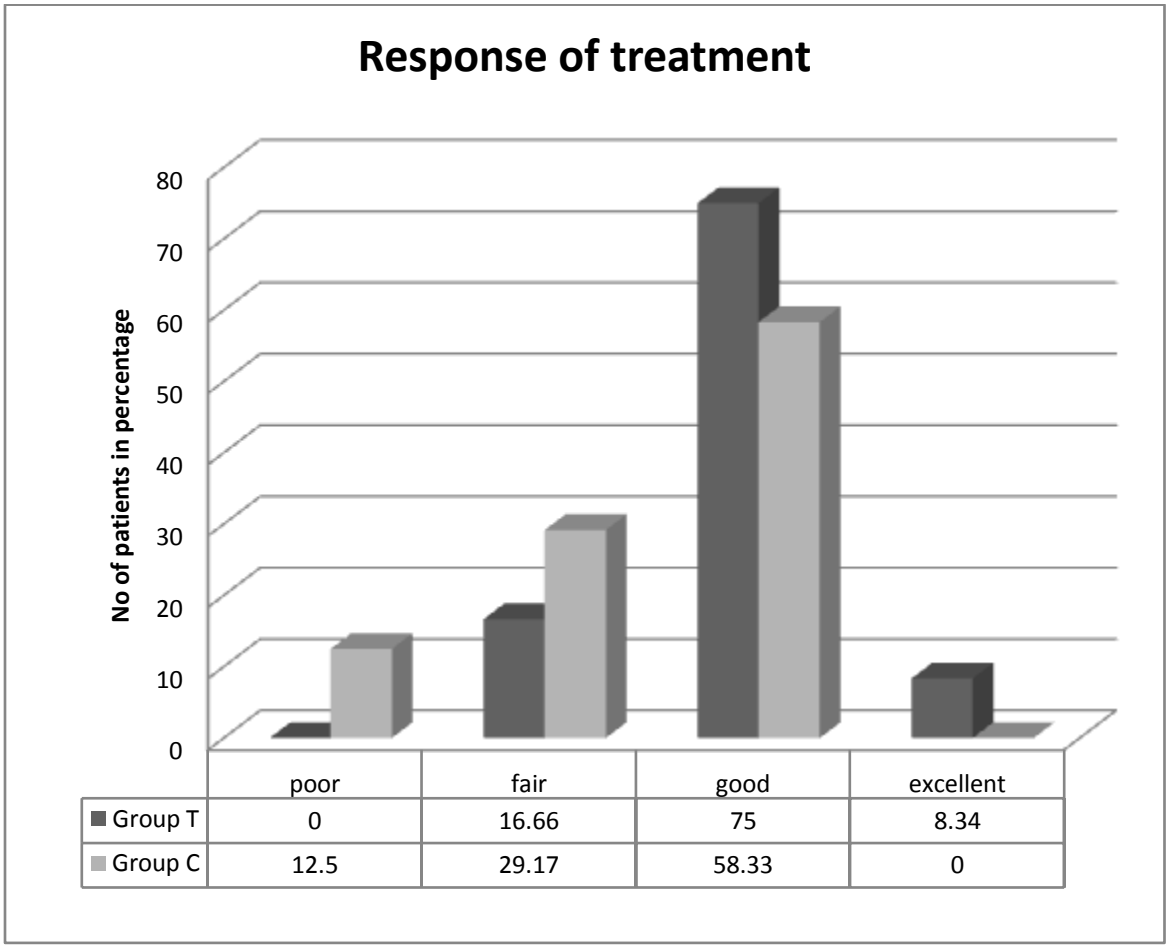

Figure 4:-

A total of 48 patients were included in the study. The mean age at treatment was 6.63 months ± 2.4 months in the Control group and 9.1 months ± 2.7 months in the timolol group.

The main indication for treatment was cosmetic.

Outcome of Timolol treatment

1. Regression was noted in the first 24 hours in 5 patients. In the remaining 19 patients, onset of regression was slightly morefaster than in the group C.
2. Regression almost always started with a change in the hemangioma color from intense red to lighter purple-blue, together with palpable softening of the lesion.
3. After this initial response, hemangiomas continued to improve as regards regression of their size, flattening of the lesion, and more evident blanching of the color.
4. At the end of the follow-up period, 8.34% of patients (n = 2) showed an excellent final response (Figure 6), with almost complete resolution of the lesion, 75% (n = 18) showed a good response with more than 50% reduction in the size of the lesion and 16.66% (n = 4) showed a fair response with less than 50% reduction in the size of the lesion. Only five patients (20.83%) were showrecurrence.
5. In general, patients with smaller hemangiomas tended to respond better to Topical Timolol.
6. However, it was difficult to analyze this relationship statistically because of the small number of patients

Outcome of Control group treatment

1. 14 of 24 patients in the group showed regression of hemangioma (Fig.4). Onset of regression varied from 1 to 12 weeks in control group. so that all 14 patients showed evidence of regression by the end of the 12 weeks.
2. The clinical course of regression was similarto that in the Timolol group as regards change in color and regression in size and depth of the lesion but the regression was very slower.
3. At the end of the follow-up period, no one (n = 0) showed an excellent final response with almost complete resolution of the lesion, 58.33% (n = 14) showed a good response, and 41.66% (n = 10) showed a fair to poor response.
4. Seven patients (29.16%) shows recurrence to treatment.

Change in refractive error

Of the 48 patients, 21 patients had significant astigmatism more than 1 D **(mean = 1.52 ± 0.73 D).** Six months after treatment, there was a reduction in astigmatic error **(mean = 0.60 ± 0.46 D).**

The reduction in astigmatic error was statistically significant in all three group

	Group T		**Group C**
No	4		10
Mean	0.75		0.85
SD	0.20		0.55
T test	**2.77**		**2.836**
P	**0.03 (P < 0.05)**		**0.01 (P < 0.05)**

Table 3:- But the reduction in astigmatism in between these two group in not significant. (P = 0.208 > 0.05)

Ptosis

Five patients had significant ptosis of more than 1 mm difference between the eyes which was resolved after the treatment.

Side effects

None of the patients developed local side effects during or after Topical Timolol.

Discussion:-

1. Our study are aimed at to find out the efficacy of timolol for the treatment of capillary hrmangioma.Capillary hemangioma occurs in about 10% of infants, with predominance in females, premature infants and Caucasians.[13]In this prospective clinical study, conducted on 48 consecutive patients with infantile hemangioma, Topical Timolol(0.5%) was shown to be almost as effective. Topical timolol was not associated with significant cardiovascular changes or local adverse effects. Because hemangiomas are very vascular lesions,accidental systemic absorption may occur. Topical timolol is given with careful cardiovascular monitoring for immediate management if significant bradycardia or hypotension occurs. Atropine would be given in the event of such a complication.However, we did not encounter such complications in topical timolol in our study.The carboxymethyl cellulose group only served as a control group to allow evaluation of our results, it works as placebo for the control group.Despite the good efficacy of timolol, relapses may occur. In this study, five patients **(20.83%)** showed evidence of rebound growth after cessation of therapy. Allof these patients were younger than 5 months at the time of starting treatment.
2. This may be explained by the fact that, in the early months of life, capillary hemangioma is in its active proliferative phase when there are high levels of proangiogenic factors. Lateron, there may be a shift of balance towards proapoptotic factors, reducing the chance of rebound growth.[11]Qin et al[14] performed one of the largest studies to date using propranolol (Beta blocker) in 58 infants with infantile hemangioma at a dose of 1–1.5 mg/kg/day. They reported a response rate of "good to excellent" in 67% of patients. In our study, we achieved a moreorlesssimilar response with topical timolol but the recurrence rate is slightly low in timolol than No treatment as shown in other studies.This suggests that topical timolol can achieve similar result to Steroid or systemic propranolol therapy. However, this would require adequate controlled double-blind studies to allow accurate comparison of the results.Furthermore, we noted a significant reduction in astigmatic error and degree of ptosis after treatment. This is consistent with previous studies reporting improvement in refractive error after systemic propranolol therapy and same things was also happened aftersteroid therapy in other study too.[18,20]

Study Limitation

Small number of patients treated.Future research should include randomized trials to confirm the effectiveness and safety of the treatment.In such cases, therapy may be continued until no further regression is noted. At a time of writing, some of the subjects were still undergoing treatment and responding well. Long term follow up is so difficult.There may be a selection bias for selecting and allocating patients in groups.

Conclusion:-

Beta blocker is relatively safe and effective for the periocular capillary hemangioma and has good success rate as steroid.

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