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HOW TOPICAL BETA-BLOCKER DID WONDER IN THE MANAGEMENT OF RESIDUAL HEMANGIOMA AFTER PROPRANOLOL THERAPY

Surgery

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ABSTRACT

Background: To determine the role of topical β- blocker in the management of residual hemangioma after propranolol therapy.
Method: A retrospective study of all pediatric patients presenting with hemangioma from April 2014 to March 2019 was performed. Topical timolol gel was applied over the residual hemangioma which persisted even after one year of propranolol therapy.
Result: Out of 68 patients included in this study 45 (70.3%), patients had complete resolution by one year using the treatment with propranolol. In 14 patients (21.8%) had residual lesion even after 1 year of treatment, upon which we applied topical timolol 0.5% gel for further 4 to 6 months. (Mean 5.35 months). At the end of the treatment, hemangioma was almost resolved.
Conclusion: Timolol is a safer alternative to propranolol for residual hemangioma as a sequential treatment. It augments the regression of residual hemangioma with minimal side effects.

KEYWORDS

Hemangioma, Propranolol, Residual lesion, Timolol

INTRODUCTION

Hemangioma is a benign tumor of endothelial cells that normally line the blood vessels, which affects 4-5% of infants. [1] Slow spontaneous involution begins at approximately 1 year of age that continues for 7-10 years. Because of benign, self-limited course, treatment is not essential in most cases but in some cases, a hemangioma can grow dramatically and destroy tissue, impair function, or even threaten the life of the patient.

Propranolol is a non-selective, adrenergic receptor blocker commonly used for cardiac ailments in young children. The efficacy of propranolol in hemangioma is excellent but the safety of propranolol therapy in infantile haemangioma has been controversial because of the systemic side effects induced by oral administration.[2] Ensuing studies have shown topical β-blocker to be effective at halting the progression of superficial hemangioma with lesser side effects.[3] The present study sought to evaluate the effect of timolol on residual haemangioma after 1 year of treatment with oral propranolol. To the best of our knowledge, no such study for the treatment of residual haemangioma has been conducted to date.

METHOD

After taking permission from the Institutes Ethical Committee, a retrospective study of all pediatric patients presenting with hemangioma from April 2014 to March 2019 was conducted. The inclusion criteria were all the pediatric patients presented with hemangioma in our outpatient department (OPD). Patients with a history of bronchial asthma, sinus bradycardia, and 2nd and 3rd-degree heart block were excluded from the study.

A total of 68 patients of hemangioma were evaluated and considered for treatment on an OPD basis. Written consent was obtained before the start of treatment and clinical photographs were taken. Each patient underwent complete blood count, blood sugar, color Doppler of the lesion, electrocardiography, and echocardiography to rule out cardiac anomalies and to know basic heart rate. The first dose of propranolol was given at a dose of 1 mg/ kg/day in three divided doses (TID) which was increased to 1.5 mg/kg/day for next two days TID if patient tolerated the drug; the dose was further increased to 2mg/kg/day TID from day three till further treatment. Patients were advised to take the drug half an hour after food and skip the drug when he missed the food for the anticipation of any untoward events of hypoglycemia. Patients were followed up at one, three, six, nine, and twelve months after the commencement of treatment. Patients were advised to continue with this treatment at home and comply with follow-up protocol. The cell phone number of the researcher was given to every patient and they were instructed to call with any inquiry. Patients who did not turn up for scheduled follow-ups were contacted on their cell phones. Patients were followed up for six months after the end of treatment. High definition clinical photographs were taken before treatment and at each follow-up visit to compare the changes accurately. Pulse rate, blood pressure, and complications if any were recorded at every follow-up visit. The dose of Propranolol was gradually tapered over two weeks at the end of therapy.

The response to the treatment was assessed using a clinical photograph as:
Group A. Excellent – More than 80% to complete resolution at or before one year.
Group B. Good - 30% to 80%resolution at/ or before one year.
Group C. Poor –Less than 30% resolution/ or before one year.

For the study, residual hemangioma was defined as hemangioma which persisted even after one year of propranolol therapy. Groups 2 and 3 were considered to have residual haemangioma.

Timolol maleate 0.5% gel two drops were applied twice daily with a finger over the residual hemangiomatous lesion in Group B which become superficial after propranolol treatment. One drop of timolol 0.5% gel has been estimated to contain 0.25 mg of timolol. Surgical excision of the hemangioma was done in Group C (poor responder). Data was entered and evaluated using Microsoft excel Version: 2019 16.0.6742.2048

RESULTS

The age at the presentation varied from one month to eight years with a mean of 24.43 months. The majority of the patients (45.5%) presented to us were below 6 months (Table1). Among 68 patients 37 patients were males and 31 were females. We noticed a slight male preponderance M/F ratio (1.19:1). Haemangioma was mostly affecting the scalp and face 48.4% followed by chest and axilla 13.2% and neck 11.7% (Table 2). In 7 patients (10.2%) there were involvements of multiple sites.

Out of 68 patients included in this study 45 (70.3%), patients had

complete resolution by one year (group A: excellent response group). 23(33.8%) patients had residual lesion even after 1 year of treatment (group B and C). 14 patients were in group B (good response group) received topical timolol 0.5% gel for further 4 to 6 months (mean 5.35 months). The site of the residual lesion in group B was mostly the face 10 (71.4%) followed by chest 2 (14.2%) and extremity 2 (14.2%). 9 patients were poor responders (group C) subsequently, underwent surgical excision. Among 45 patients treated with propranolol (excellent responders), 31(68.8%) showed a complete resolution in six months of treatment, and in 6 (13.3%) and 8 (17.7%) patients, treatment was continued for 9 and 12 months respectively. At the end of the treatment haemangioma was completely resolved in group A and group B (Fig1, 2, 3) Therefore 59 out of 68 (86.7%) cases were resolved at the end of treatment. We did not observe any side effects of propranolol in our patients. Three patients had complained of pruritis while on timolol therapy. There was no recurrence of hemangioma in follow up visit after six months.

DISCUSSION

Hemangioma is characterized by its dramatic growth and development into a disorganized mass of blood vessels. We noticed almost equal male to female ratio in our study although in many studies there was female predominance [4, 5] Although hemangiomas may occur on any part of the body, they demonstrate a striking predilection for the head and the neck region [6] also noticed (48.4%) in the current study.

Nearly 40% of children require further medical or surgical intervention because of bleeding, ulceration, visual axis and airway obstruction, high-output cardiac failure, or risk for permanent disfigurement [7].

Propranolol has been in use recently in the treatment of hemangioma owing to its better efficacy and good tolerance hence, considered by most authors to be the first-line therapy. Its role was discovered accidentally in 2008 while treating a newborn with obstructive hypertrophic cardiomyopathy having synchronous hemangioma.[8]

An effective therapeutic dose commonly used for propranolol (2 mg/kg/day) is usually recommended for focal and segmental infantile hemangiomas in infants younger than 6 months however, optimal dose, as well as the duration of treatment, is still unclear. The dose of propranolol varies between 2 to 4 mg/kg/day [9, 10] and the duration of treatment varies between 7 to 12 months. [11] In a case series, Pratico et al reported that about 10% of patients with infantile Cutaneous Hemangiomas treated with propranolol have re-growth, slow improvement, or failure.[12] Even with the treatment with propranolol in hemangioma, the residual lesion is a concern. In one study there was 20% of patients had residual lesion termed as poor responders. [13] In our study, twenty-three patients (33.8 %) had residual lesions even after 1 year after propranolol treatment.

The safety of propranolol therapy in infantile haemangioma has been controversial because of the systemic side effects induced by oral administration. Although, common systemic side effects including bradycardia, bronchospasm, hypotension, hypoglycemia, electrolyte disturbances, and diarrhea, are usually self-limiting without intervention. [2] Concerns regarding the potential effects of propranolol on neurocognitive ability have been raised recently. [14, 15] Phillips et al studied 188 infants with infantile hemangiomas. Gross motor abnormalities were reported in thirteen patients and delayed walking was observed in seven other children on long-term use of propranolol. It is widely known that the lipophilic nature of propranolol could favour in penetrating the blood-brain barrier. Consequently, researchers attempted to use another β –blocker eg, timolol which is applied topically in hemangioma with fewer side effects.

The use of timolol has been documented in many studies with good results. [16, 17, 3] All were given in the early proliferative phase of hemangioma. Timolol mainly stimulate the contractility of Hemangioma pericytes which accelerate the involuting phase of hemangioma. Topical application of timolol facilitates local drug distribution and reduce the release of the drug into the blood circulation hence associated with less side effect. [18] Considering this, we switched over to the timolol application after one year of treatment with propranolol. We have used topical timolol gel on residual lesion after propranolol treatment for 1 year. The systemic absorption of timolol maleate gel formulation is considered to be significantly less than that of timolol maleate solution and hence has been favoured in one study.[19] Future prospective trials involving a larger number of patients and a longer follow-up period should be addressed to determine whether this sequential therapy of propranolol followed by timolol for residual haemangioma effectuates its therapeutic promise.

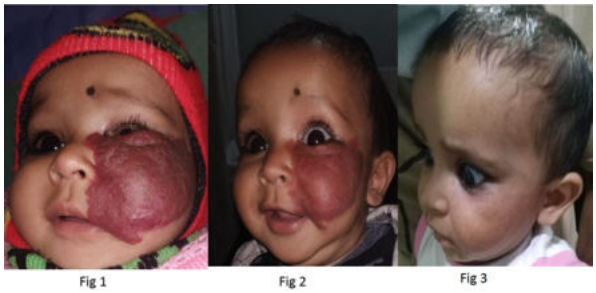

Fig 1 Fig 2 Fig 3

Fig1- Photograph of the patient before start of propranolol
Fig 2 - Residual lesion after propranolol
Fig 3- Photograph of the patient after timolol application

Table-1 Age wise distribution of hemangioma

AGE	Number	Percentile (%)
Less than 6 month	31	45.5
6 month to 12 months	22	32.3
More than 12 months	15	22
Total	68	

Table- 2Distribution of hemangioma over the body

Area of involvement	Number n=68 (%)
Scalp	12 (17.6)
Face	21(30.8)
Neck	8 (11.7)
Chest & axilla	9 (13.2)
Upper limb	5 (7.3)
Lower limb	5 (7.3)
Abdominal wall	2 (2.9)
Multiple sites	6 (8.8)

CONCLUSION

We found that topical timolol can be used as an alternative to propranolol for residual hemangioma as a sequential treatment. It augments the regression of residual hemangioma with minimal side effects and prevents recurrences.

Contributor's detail

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