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Case Series

Topical timolol for treatment of pyogenic granulomas in children: A case series

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Abstract

Background: Pyogenic granuloma (PG) is benign vascular tumour presenting as small, friable, reddish papule or nodule. Bleeding tendency of PGs warrants their removal.Various available treatment options require local anesthesia, cause pain, local side effects, scarring and become undesirable for treating children. Hence, topical beta blocker (timolol 0.5%) becomes a valuable option for treating PG in children.
Methods: We enrolled 3 healthy children aged less than 14 years with clinical diagnosis of PG for the case series. Patients with any cardiopulmonary abnormalities were not enrolled. All the patients were prescribed 0.5% ophthalmic solution, topically twice a day for 6 weeks. Due to the prevailing COVID-19 pandemic, patients were called for follow up visits every three weeks. At the end of 6 weeks, patients were evaluated for the improvement and followed up for one year after treatment to look for any recurrences or any long-term side effects of timolol.
Results: All three patients enrolled in the study showed partial improvement at 6weeks and complete improvement in two patients after one year. No recurrence or any long-term side effects with timolol were noted in any patient.
Conclusions: Topical beta blocker (Timolol) is easy to administer, safe and noninvasive. It appears to have a promising role in children with no recurrences or any associated long-term side effects.

Keywords: Beta blocker, children, lobular capillary haemangioma, pyogenic granuloma, timolol, vascular tumour

Introduction

Pyogenic granuloma (PG), named as lobular capillary hemangioma is common in children[1].As PG has tendency to bleed, its removal is frequently considered[2]. PGlocated on face is of cosmetic concern[2, 3]. Several treatment options like surgical removal, curettage and

cauterization, laser and topical Imiquimod [2, 4, 5, 6] are undesirable for treating children and lesions located over nail matrix and gingivae.Hence, topical timolol becomes a valuable treatment option for PG [7] to avoid procedure related complications in children[3, 8]. Herein, we report our experience of topical timolol in 3 cases of PG in children.

Report of cases

We enrolled 3 healthy children of pyogenic granuloma coming to the Dermatology OPD in 2020 and 2021 for the case series after taking informed consent. Children were diagnosed with pyogenic granuloma on the basis of clinical features. No biopsies were carried out. Patients were prescribed timolol maleate 0.5% ophthalmic solution topically, one drop twice a day for 6 weeks and were followed up every 3 weeks due to prevailing COVID 19 pandemic. Patients with cardiopulmonary abnormalities were not included in the study. At the end of 6 weeks, complete resolution of the lesion was considered as complete improvement, more than 75% decrease in size was considered as partial improvement and no change in size was considered as no improvement.

There were two females and one male child aged 1.5 to 14 years. The clinical characteristics of the patients and their response to treatment with follow up are presented in [Table1]. [Figure 1a, 2a, 3a] and [Figure 1b, 2b, 3b] show clinical features of all three patients respectively at the time of presentation and after 6 weeks of treatment. All patients showed decrease in size and bleeding. At 6 weeks no local or systemic side effects like changes in the blood pressure, blood glucose and ECG were noted. Patients were followed up after one year. Patient 2 was lost to follow up. Patient 1 and 3 showed complete improvement and showed no recurrence or any long-term side effects. [Figure1c, 3c] show the images of patients with complete improvement after one year.

Table I: Clinical profile of the patients and response to treatment

Patient	Age (year)	Sex	Location	Duration of lesion	No. of lesions	Largest diameter (cm)	Clinical features at presentation	Clinical outcome at 6wks	Clinical outcome after 1 year follow up	Adverse Effects after 6 weeks and after 1year follow up
1.	4	F	Face (upper lip)	1.5 months	1	2.5cm	Well defined round plaque covered with haemorrhagic crust	Partial* Improvement	Complete improvement	Nil
2.	1.5	F	Face (right cheek)	1 month	1	1cm	Well defined red plaque covered partiallywith haemorrhagic crust	Partial improvement	Lost to follow up	Nil
3.	13	M	Face (nasolabial fold)	1 month	1	1cm	Well defined, red, polypoidal nodule covered with yellowish and hemorrhagic crust	Partial improvement	Complete improvement	Nil

F-Female
* >75% reduction in size
M- Male

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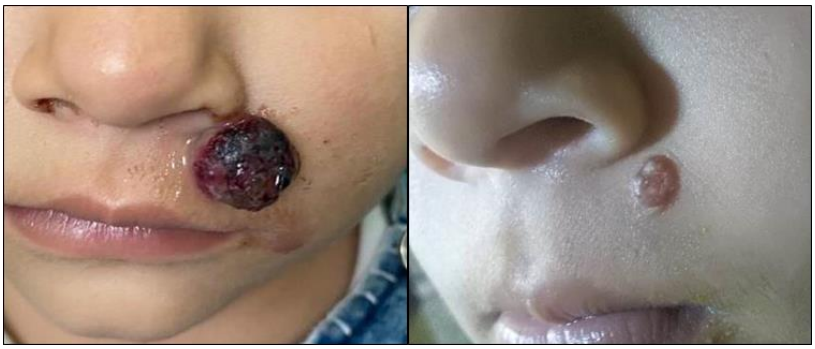
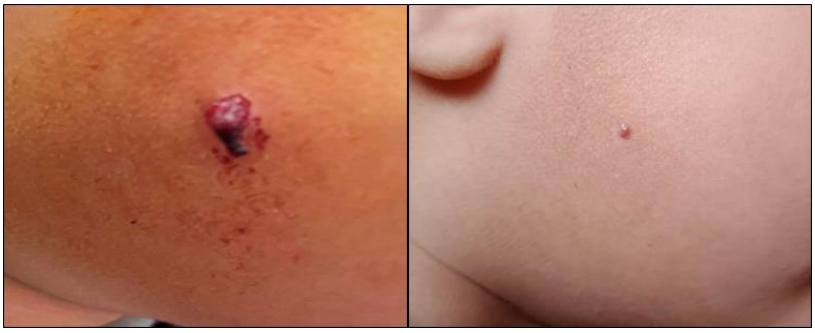
Figure1a, 2a, 3a show the clinical picture at the time of presentation and figure 1b, 2b, 3b show the improvement after using topical timolol for 6weeks. [Figure1c, 3c] show the images of patient1 and patient 3 with complete improvement after one year.

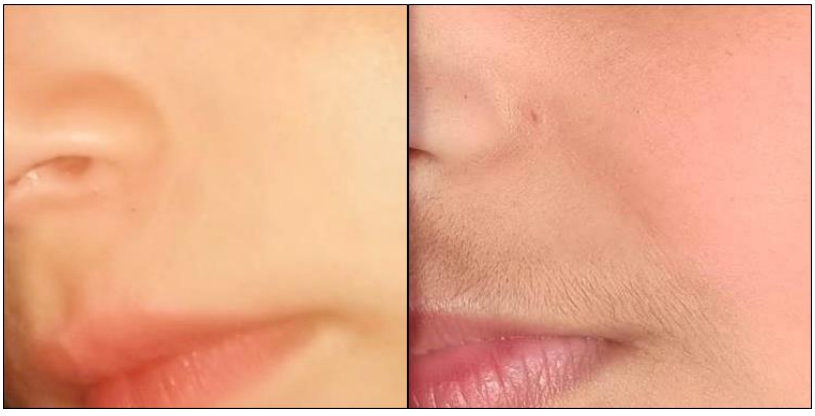


(1a) **(1b)**



(2a) **(2b)**

(3a) **(3b)**



(1c) **(3c)**

Discussion

Pyogenic granulomas are rapidly growing benign vascular tumours [1] usually located on the skin or mucosa, frequently seen on face and fingers with a slight predominance in women. They are commonly seen in children with less than five years of age on head and neck region. Rarely spontaneous resolution can be seen, but mostly treatment is required to prevent bleeding and secondary infection. Multiple destructive treatment options like electrocautery, curettage, cryotherapy, excision with primary closure, shave excision, injection of sclerosing agents and various laser modalities are available[2,4,5,6,9]. However, these treatment options are associated with pain, local side effects, and are difficult to perform in pediatric patients. Surgical excision requires local anesthesia, can cause scarring[2], lasers treatment requires multiple sittings and depth of penetration varies with different lasers and thus the targeting of vessels can be affected[4, 5]. Topical 5% imiquimod takes a long duration for response and causes erythema, edema, crusting, superficial scars, and dyspigmentation[10].

Our case series showed partial improvement (>75% reduction) in all three patients after 6 weeks of treatment with topical timolol. Previously, Gupta *et al*.[7] observed complete improvement in 4 patients, partial improvement in 3 patients and no improvement in 4 patients after 10 weeks of treatment. Lee *et al*.[2] found complete improvement in two patients and partial improvement in 5 patients. Response to treatment was seen at variable durations from 6weeks to 6 months. There one patient with complete improvement was on oral propranolol. While Lee *et al*. [11] used oral propranolol in a child with multiple subcutaneous PGs which showed initial improvement followed by no resolution of lesions. None of the studies reported any side effects of topical timolol.

Our case series had all children less than 14 years of age. Gupta *et al*.[7] had patients aged more than 14 years of age. We used topical timolol 0.5% twice a day while Gupta *et al*. used four times a day and Lee *et al*. [2] used three times a day in most of the patients. These differences along with less number of patients in our case series can explain the variability of results.

We followed patients after one year, patients showed complete improvement of the lesions. Delayed effects on the lesions can be explained on the understanding that PG have short proliferative phase. Treatment given for a brief period may induce apoptosis and lead to continued regression of lesion, even when the treatment is discontinued. Long term effects of timolol causing apoptosis can explain the delayed effect[2].

Beta receptors present on the endothelial cells cause vasodilation, inhibit the endothelial cell apoptosis and expressproangiogenic factors like VEGF(Vascular endothelial growth factor) and bFGF (basic fibroblast growth factor)[15]. These angiogenic factors are mainly expressed by the endothelial cells and pericytes in oral haemangiomas, while in PG local inflammatory cells like macrophages and fibroblasts mainly express these[2].

Topical timolol is a nonselective beta- blocker, recently documented in the management of superficial hemangiomas. It is available as a 0.5% ophthalmic solution or gel preparation. It acts by causing vasoconstriction, decreased vascular growth factors, and decreased blood flow into the hemangiomas, thereby inhibiting the growth and proliferation of vascular tumours[2, 12].Since same kind of features underlie both infantile hemangiomas and PGs, beta blockers can be equitably effective in both[12].

Timolol has varying effects on pyogenic granulomas as beta adrenergic receptors are expressed weaklyin around 50% of cases of PGs[12]. It is also speculated that the fibrous component in PGs increases with time and persists. Therefore, timolol is effective in early onset lesions and in those patients which express beta receptors[7]. If no improvement is seen then a differential diagnosis for red nodule must be considered. Most common differential diagnosis is amelanotic melanoma, but that is rarely seen in children. Histopathology should be considered for the confirmation of diagnosis. Side effect profile of topical timolol is favourable in pediatric or adult age groups. Systemic bioavailability of topical timolol is not likely to exceed 25%, making an equivalent dose of 1-2.5mg of oral propranolol[13, 14].

In conclusion, our case series showed encouraging results of topical beta blocker (timolol) in

the treatment of PG in young children. Our observations are in line with previous case reports and series. It appears a promising, safe, affordable and noninvasive treatment modality for the treatment of PG in children.It can be used as a supplementary therapy before considering surgical removal of the lesions. Long term follow up of the patients showed further improvement and no side effects. Main limitations of our series were the small number of patients. More studies with long follow up are required to decide the minimum effective dose and duration of treatment and report the long-term effects and recurrences.

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