

Original Article

Topical timolol maleate combined with oral propranolol in treatment for nasus externus infantile hemangiomas: a retrospective study of 17 cases

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Abstract: The aim of our study was to assess the efficacy and safety of topical timolol maleate combined with oral propranolol for nasus externus infantile hemangiomas. Between March 2012 and May 2014, propranolol was given orally to 17 infants with proliferating hemangiomas in a dose of 1.0-1.5 mg/kg/day in our department and dipped topically a small amount of 0.5% timolol maleate eye drops with medical cotton swabs on hemangiomas lesion area of the children twice a day by every 12 hours. There were 6 males and 11 females aged from 2 months to 11 months with a median of 5.4 months. The lesions were located in the nasus externus region, and measured 0.5 cm × 0.5 cm-2.5 cm × 2 cm in volume. The therapy duration was planned for 6-8 months or the two drugs were stopped when complete regression of lesions was obtained. The therapeutic outcomes and safety were assessed by the changes of color, size of tumor, and adverse effects throughout the course of treatment. The mean therapy duration was 22.8 weeks ranged from 3 to 8 months. Of 17 the patients, 13 demonstrated excellent response, 3 showed good response, and 1 displayed moderate response. No major collateral effects were observed. Oral propranolol combined with topical timolol maleate might be used as the first-line treatment selection in the treatment of nasus externus infantile hemangioma.

Keywords: Nose, infantile hemangiomas, timolol maleate, propranolol

Introduction

Hemangioma is a congenital benign tumor originating from residual embryonic angioblasts. Infantile hemangiomas (IHs) is the most common, benign, self-limiting tumor of infancy and therefore needs no treatment [1-4]. The tumor has a unique life cycle that is divided into three phases: proliferative, involuting and involuted. It is commonly located on the face such as nose [5]. Nasus externus hemangioma is the common in the facial hemangioma in children. Generally, active surgical treatment was not recommended for hemangioma. However, treatment is necessary when the hemangioma appears on the nose. Their rapid growth may be alarming and deforming, with distortion of adjacent nasal structures (nostrils, alar cartilage) that can have long-term residual effects. In addition, the obvious visible deformity in the center of a child's face presents a severe emo-

tional burden initially for the parents and secondarily for the child as peer curiosity and ridicule are directed toward the deformity. These lesions regress naturally, impacting on cosmetic outcome. In addition, early intervention may relieve the mental burden of the parents and avoid casting an unpredictable psychological shadow on the child. Thus, a judicious early intervention therapy is necessary to accelerate the disappearance of hemangioma and reduce potential complications.

Our group used the method of topical timolol maleate combined with oral propranolol to treat nasus externus hemangioma in 17 patients, and achieved ideal results. This is one of few prospective studies. No treatment failure was observed in any patients in this study who were able to continue the administration of topical timolol maleate combined with oral propranolol. Topical timolol maleate combined with oral

propranolol proved to be well tolerated, safe, and without considerable complications when used in infants.

Patients and methods

Patients

Twenty-two patients with nasus externus proliferating hemangioma were treated with topical timolol maleate combined with oral propranolol from March 2012 to May 2014 at the Department of Oral and Maxillofacial Surgery, hospital of Stomatology, China Medical University. They were 6 boys, 11 girls, mean age 5.4 months (range, 2~11 months). The volume of these tumors varied from a minimum size of 0.5 cm × 0.5 cm and a maximum size of 2.5 cm × 2.0 cm. The tissue deformation also caused a visible deformity on the nose. The diagnosis of hemangioma was made based on the medical history, clinical presentations, and Doppler ultrasonography scan. Patient files were collected, including clinical characteristics, efficacy of treatment, and adverse reactions. Our inclusion criteria for this study were as follows: 1. No infants were given any treatment before our treatment; 2. Any other vascular malformations were excluded, using the classification and nomenclature of vascular anomalies proposed by Waner and Suen [4]; 3. Normal chest X-ray, electrocardiogram, blood coagulation, liver function, renal function and blood routine examination. The ethical review board of China Medical University approved the study and all the infants' parents provided written informed consent.

Treatment protocol

Informed consent was obtained from the parents of the infants after informing them of the treatment protocol and side effects of timolol maleate and propranolol. All the patients were admitted to the hospital and hemangiomas were in the rapid proliferating phase. Propranolol (10 mg/tablet, Tianjin Lisheng Pharmaceutical Co. Ltd) was prepared from tablet to a suitable solution at a dose of 1.0-1.5 mg/kg/day (the ones who are younger than 3 months took 1.0 mg/kg, older 3 months took 1.5 mg/kg), in once dose. And dipped topically a small amount of 0.5% timolol maleate eye drops (25 mg/5 ml, Wuhan five King Pharmaceutical Co. Ltd. China) with medical cotton swabs on hem-

angiomas lesion area of the children twice a day by every 12 hours, and erythromycin ointment was applied around the lesions to prevent the timolol from leaking. For the first 3-5 days of management, blood pressure, heart rate, and blood glucose levels were monitored at the inpatient ward. The patients who suffered from no adverse reactions were given it orally by their parents or guardians after discharge. Close observation was given to patients' heart rate, blood pressure and other vital signs during the treatment and parents should notice whether local redness appear, and whether their children had such symptoms as loss of appetite, nausea, vomiting, wheezing, shortness of breath, lethargy, diarrhea. Once any symptom appears, stop using these drugs immediately and observe carefully. The patients should be ordered to be reexamined periodically in order to observe the size and color of hemangiomas for assessment of curative effect. The dose of the drug was altered according to their weight changes and the degree of adverse reaction at the period of following up. Treatment was continued till the age of 1 year unless complete resolution occurred. The follow-up timeline extended from 6 month to 12 months (median: 8.5 months). Data was obtained by investigating the patients' medical dossiers. Photographs that had been taken were assessed.

Evaluation of efficacy

The therapeutic outcome was evaluated with Doppler ultrasonography scan. The results were measured by the hemisphere measurement and photographs [6]. The clinical effect of treatment was graded on a 4-point scale proposed by Achauer et al [7]. Based on improvement in volume, color, and texture after treatment: scale I (poor)-tumor volume decreased by less than 25%; scale II (moderate)-tumor volume decreased between 26% and 50%; scale III (good)-tumor volume decreased between 51% and 75%; and scale IV (excellent)-tumor volume decreased between 76% and 100%.

With regard to safety, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood glucose were close monitored in the course of 3-day hospitalization and recorded one hour after each dose. Local side effects such as rash, red spots, erosion, and ulceration were also close observed.

Timolol maleate combined with propranolol treatment for nasus externus IHs

Table 1. Summary of treatment of nasus externus IHs with topical timolol maleate combined with oral propranolol

Patient No.	Sex	Age at Treatment Onset (mos)	Treatment Duration (weeks)	Size of IH before Treatment	Size of IH after Treatment	Side Effects	Follow-up (mos)	Response
				Length/width, cm	Length/width, cm			
1	F	4	16	1.5/1	0/0	No	6	Excellent
2	F	7	24	1/1	0.5/0	No	6	Good
3	F	2	20	1/0.5	0/0	No	10	Excellent
4	M	11	32	2.5/2	0/0	No	10	Excellent
5	M	4	16	2/1.5	1/0.5	Diarrhea	10	Moderate
6	F	3	28	1/1	0/0	No	8	Excellent
7	M	2.5	12	1.5/1	0.5/0	No	10	Excellent
8	F	6	32	2.5/2	1/0.5	No	6	Excellent
9	F	9	24	1.0/1.0	0/0	No	6	Excellent
10	F	8	16	1.5/1.5	1/0.5	No	8	Good
11	F	4.5	32	2/1	0/0	No	10	Excellent
12	M	2	20	2/0.5	0.5/0	No	8	Excellent
13	F	2	32	1/1.5	0/0	No	12	Excellent
14	F	4	28	2/1	0.5/0.5	No	7	Good
15	M	6	16	1/0.5	0/0	No	8	Excellent
16	F	10	28	2/1	0/0.5	No	10	Excellent
17	M	7	12	1/1	0/0	No	10	Excellent



Figure 1. A 9-month old girl with an infantile hemangioma in the right ala nasi area. A: Before treatment. B: 24 weeks after topical timolol maleate combined with oral propranolol treatment, the tumor has completely disappeared.

Statistical analysis

All data was entered into a database and processed using the Statistical Package Social Sciences (SPSS version 18.0; SPSS Inc, Chicago). Kruskal-Wallis test was used to compare the differences of the average heart rate, systolic blood pressure, and diastolic blood pressure between that of before and after drug administration. There was significant difference if $P < 0.05$.

Results

After 6 months to 12 months of follow-up, the final results were as follows: The hemangiomas were well controlled in all cases. All of them decreased in size after treatment. Efficacy was evaluated as follows: scale IV (excellent), 13 cases (76%); scale III (good), 3 cases (18%); scale II (moderate), 1 case (6%); and scale I (poor), 0 (0%). The parents were quite satisfied with the results. The majority of the tumor dis-



Figure 2. A 11-month old boy with a infantile hemangiomas in the apex nasi area. A: Before treatment. B: 32 weeks after topical timolol maleate combined with oral propranolol treatment, the color of tumor has faded and volume reduced.

Table 2. Heart rate and blood pressure at baseline and propranolol and timolol maleate initiation period (Mean \pm SD)

	Baseline	Day 1	Day 2	Day 3
HR (beats per minute)	125.3 \pm 12.3	123.5 \pm 10.5	124.6 \pm 9.8	124.2 \pm 11.6
SBP (mmHg)	83.7 \pm 10.1	84.1 \pm 12.9	84.8 \pm 15.1	85.2 \pm 16.7
DBP (mmHg)	57.9 \pm 13.6	57.7 \pm 16.1	56.6 \pm 14.8	55.9 \pm 12.9

appeared, resulting in an overall improved deformity status. At 24 hours post-medication, the tension of the tumor surface of most children decreased and the texture became softer. 2 cases of the patients took drug for 12 weeks, 4 cases for 16 weeks, 2 cases for 20 weeks, 2 cases for 24 weeks, 3 cases for 28 weeks, 4 cases for 32 weeks, mean time 22.8 weeks. One of the tumors regressed completely after treatment. However, the tumor had relapsed when the infant was followed up 8 weeks later and the proliferation was effectively controlled by continuation of medication (**Table 1**). The typical cases are shown in **Figures 1** and **2**. No infants were withdrawn from the treatment study due to side effects. In all 17 infants the heart rate slowed, blood pressure dropped, and rate of breathing slowed after starting to treatment. However, all these signs returned to normal after they had taken propranolol for more than 12 h ($P>0.05$, **Table 2**), and none required special treatment. There were no severe gastrointestinal adverse reactions. No severe adverse effect was observed.

Discussion

Hemangioma is a common benign tumor in infants that may disappear spontaneously. However, the development of hemangioma is unpredictable. Although natural involution may occur, growth and hypertrophy may cause a distortion of the nasal architecture or present emotional problems necessitating treatment. In case of spontaneously involuting hemangiomas, half of the children do have some residual cosmetic deformity that will need surgical interventions in their subsequent adult life. There could be some degrees of scarring, a fibrofatty residuum, and cutaneous blemish [8-10]. Thus, intervention therapy is necessary to accelerate the process of hemangioma treatment. Obstructed nasal airways, bleeding, and severe deformity of the adjacent cartilage or nasal bones that lead to growth abnormalities are absolute indications of topical timolol maleate combined with oral propranolol to treat nasus externus hemangioma. Parental anxiety and the diagnosis of a vascular malformation (usually noninvoluting) are secondary considerations.

Irradiation and pressure are probably contraindicated because of possible chronic injury to underlying cartilage and bone, resulting in later growth disturbances. Similarly, the use of inter-

feron alpha is probably not indicated except for massive or life-threatening lesions [11]. Sclerotherapy with agents such as a hypertonic saline solution, sodium tetradecyl sulfate, and the like, may be effective [12, 13], but their use is difficult and painful in the nose. The intraleSIONal administration of steroid may be effective in causing a cessation of growth, blanching of color, and initiation of subsequent involution [14, 15]. In 2008, Léauté-Labreze et al. used propranolol (2 mg/kg/day) to treat hypertrophic cardiomyopathy, and accidentally discovered that propranolol controls hemangioma in the nasus externus cavity very effectively [16]. The same result has been observed in nine other patients with facial hemangioma. The underlying mechanism of hemangioma possibly involves the β receptor antagonist, which can induce endothelial cell apoptosis, down-regulate the gene expression of VEGF and bFGF, and prevent vasoconstriction. Therefore, the novel finding of Léauté-Labreze et al. on propranolol is considered a milestone in hemangioma treatment [17]. In the study of Léauté-Labreze et al, a dose of 2 mg/kg to 2.5 mg/kg propranolol was used. In the current research, based on the study of Qing et al from the Shandong Linyi Tumor Hospital, at a dose of 1.0-1.5 mg/kg/day (the ones who are younger than 3 months took 1.0 mg/kg, older 3 months took 1.5 mg/kg) were administered and comparable results were obtained [18]. Guo and Ni were the first to reveal successful outcomes following the use of timolol solution in the treatment of a 4-month-old infant with superficial capillary hemangioma of the eyelid in 2010, the markedly low rate of adverse reactions to topical timolol maleate treatment reported thus far suggests that it is a safer alternative to systemic propranolol [19, 20]. However, to date, there have been relatively few studies on timolol treatment for IHs, and the majority of these are case reports. Semkova and Kazandjieva described the initial phase of a prospective study, which evaluated the efficacy and safety of topical 0.1% timolol gel for patients with IHS [21]. In the present study, erythromycin ointment was applied to prevent timolol leakage around the lesions and this may have increased the duration of drug action and improved the drug efficacy. The short-term results were excellent, and the side effects were minimal, we did not encounter any serious untoward side effect that could dictate discontinuation of the therapy. Our experience conforms to most of the published literature where safety of proprano-

lol and timolol maleate in infants has been well established.

In view of the new theories for pathogenesis, possible explanations for the therapeutic effect of such β -blockers as propranolol and timolol maleate on IHs may include vasoconstriction due to decreased release of nitric oxide, which results in the early visible change in color and is associated with a palpable softening of the hemangioma [22]. Decreased expression of proangiogenic factors like vascular endothelial growth factor and β -fibroblast growth factor may occur through the down regulation of the Raf-mitogen-activated protein kinase pathway, matrix metalloproteinase 9 secretion, and human brain microvascular endothelial cells tubulogenesis, which explains the progressive improvement of the hemangioma, possibly through the triggering of apoptosis of capillary endothelial cells, which results in further tumor involution [23-25].

Our results of the treatment with topical timolol maleate combined with oral propranolol for nasus externus IHs are excellent with a success rate of 76%, without the obvious adverse events. These percentages are the same as those reported in the literature. Often, the amount of timolol maleate and propranolol that were administered in those cases is also difficult to establish. We tried my best to treat all patients in a standardized manner. We reasonably strive to conclude according to reports of domestic scholars and our considerable clinical experience that propranolol 1.0 mg/kg for the patients aged less than 3 months and 1.5 mg/kg for the ones aged more than 3 months are safer dosage ensuring safety of patients. But still we suggest that it should be necessary for an infant to have a detailed general examination before propranolol is prescribed. In addition, all infants should be in the inpatient hospitalization under observation for 3 to 5 days after the first treatment, and blood pressure, heart rate and adverse reactions were closely monitored.

There are many methods for treating a hemangioma. A precise diagnosis as well as a proper and comprehensive treatment can achieve ideal outcomes and improve the quality of life of patients. Most researchers have focused on comprehensive treatments such as medication, surgery and injection combination, as well as laser and drug applications. However, although novel treatment combinations have

some advantages, the risk for complications or side effects also has to be taken into account [26, 27]. This study showed that topical timolol maleate combined with oral propranolol therapy is a very safe herapeutic method in the treatment of nasus externus IHs as no severe complications were observed by us. Since IHs is a self-limiting tumor, the expectation is that function and clinical appearance would eventually improve, but we were able to demonstrate that when the nose is at risk of apnea impairment, topical timolol maleate combined with oral propranolol therapy is highly effective: all examinations improved after treatment.

Today there is an increasing interest on topical timolol maleate combined with oral propranolol in the treatment of nasus externus IHs with promising results and until now few reported side effects. We think that it has almost become the first choice of treatment. We conclude that topical timolol maleate combined with oral propranolol therapy has a valuable place in the treatment of nasus externus IHs. Long-term result analyses, withdrawal symptom observations, and comparison studies are required in future research.

In conclusion, a small dose of topical timolol maleate combined with oral propranolol for nasus externus infant hemangioma yields remarkable clinical results and rare side effects. Topical timolol maleate combined with oral propranolol use is safe, simple, and effective for the treatment of hemangioma in infants.

Acknowledgements

The clinical study was approved by the China Medical University Review Board and informed consents were signed by the children's parents in all instances.

Disclosure of conflict of interest

None.

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