Clinical Report

Oral Propranolol Combined with Topical Timolol Maleate for the Treatment of Compound Infantile Hemangioma in Parotid Region

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Abstract: The aim of the study was to investigate the clinical results and safety of oral propranolol combined with topical timolol maleate for the management of infantile hemangioma in parotid region. Between October 2014 and June 2017, 25 infants with parotid hemangiomas were treated with a combination of oral propranolol and topical timolol maleate. There were 10 males and 15 females, aged from 2 to 10 months with a mean age of 4.5 months. Propranolol was administrated at a dose of 1.0-1.5 mg/kg body weight, and the drug was taken once per day. All lesions were also administrated using topically timolol maleate in every 12 hours. The blood pressure, heart rate values, and adverse events were recorded during hospitalization. The electrocardiogram was reviewed one month after discharge. 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 5.6 months ranged from 3 to 10 months. Of 25 the patients, 17 demonstrated excellent response, 8 showed good response. The heart rate, systolic blood pressure and diastolic blood pressure were all decreased to some extent in the children after administration, but the difference was not statistically significant (all P > 0.05), and also was not associated with any clinical symptoms. No serious adverse effects were encountered. Oral propranolol combined with topical timolol maleate was an effective treatment for infantile parotid hemangioma with minor side effects, and might be used as the first-line treatment selection.

Keywords: Propranolol, Timolol maleate, Compound, Parotid, Hemangioma

Introduction

Infantile hemangiomas (IHs) is the most common benign tumor of parotid tumor in children, which is composed of proliferating endothelial cells. The typical clinical characteristic is rapid proliferation within one year after birth and slowly subsiding later. According to the classification of hemangiomas by Warner and Suen, the hemangioma is usually divided into 3 basic subtypes, including superficial hemangioma, deep hemangioam and compound hemangioma. Although the majority of IHs eventually involute, a small number of fast growing tumors, especially on the special of the face, the results are often difficult to predict. The parotid region is an frequently involved part of infantile hemangioma. Severe parotid region hemangioma not only affects the appearance of children, but also can cause ulceration, ulceration, infection and other complications. Long-term external compression of external auditory canal can cause external auditory canal stenosis, and further affect the development of children's hearing. Therefore, active treatment is needed. Currently, non-selective β adrenergic receptor blocker has become the first-line treatment choice for IHs, including systemic propranolol, nadolol, and topical timolol maleate. Each drug has its particular advantage and limitation. Many clinical studies have confirmed that propranolol is usually highly effective for deep hemangiomas and timolol maleate is usually highly effective for superficial lesions. In this retrospective study, a combination of both drugs was developed for compound lesions of parotid region in our department since October 2014 and achieved satisfactory results. Here was reported as follows.

Materials and Methods

Patients and methods

Twenty-five compound parotid IHs were treated with oral propranolol combined with topical timolol maleate at the Yantai Stomatological Hospital from October 2014 to June 2017. There were 10 males and 15 females, with an average age 4.5 months ranged from 2 to 10 months, and the surface area of the hemangioma was 2 cm × 2.5 cm to 5 cm × 6 cm. All the lesions were diagnosed based on history, clinical manifestations, Doppler ultrasonography or Magnetic resonance imaging (MRI). Inclusion criteria: Compound hemangioma of parotid region, resulting in facial asymmetry and potential functional damage; No other treatments for hemangioma previously, such as steroids, lasers, and so on. Exclusion criteria: Bradycardia, secondary and above atrioventricular block, arrhythmia, congestive heart failure and other diseases; Asthma, bronchitis, obstructive pulmonary disease. Informed consent was signed by the parents of all children and this clinical study was approved by the Yantai Stomatological Hospital Review Board.

All children were examined by echocardiography, electrocardiogram, the blood routine and the clinical photographs were obtained before administration. Propranolol (10 mg/tablet, Tianjin Lifeng Pharmaceutical Co.Ltd China) was orally administered half an hour after feeding at a dose of 1.0 to 1.5 mg/kg (1.0 mg/kg for ≤3 months, 1.5 mg/kg for> 3 months) once daily. The 0.5% timolol maleate eye drops (25 mg/5 ml, Wuhan five King Pharmaceutical Co. Ltd. China) were gently coated onto the hemangioma area in a thin layer using a medical swab. The ophthalmic solution was applied twice daily at intervals of 12 hours. During a short hospitalization of three days, the
The tumor has almost disappeared.

Approximately 45% of the lesions were present at birth, three out of four was unilateral, and 86% were compound hemangioma. Although most hemangiomas do not require treatment, hemangiomas located in the parotid region, especially in the rapid growth phase, are often accompanied by a series of complications, including facial asymmetry, ulcers, and massive bleeding. Compression of external auditory canal for a long time affects hearing and language development of children, and even causes obstruction of respiratory tract and endangers life. At present an active early intervention is increasingly accepted, so as to shorten the course of its natural course and reduce unnecessary complications. The traditional treatment methods include drug therapy, laser therapy and surgery, with drug therapy being the mainstay of treatment. The individualized treatment should be dependent on the location, depth, range, and growth stage of the hemangioma, in order to obtain the best therapeutic effect. Laser therapy is only suitable for

| Table 1. Heart rate and blood pressure at baseline and propranolol combined with timolol maleate initiation period (mean ± standard deviation). |
|-----------------|-----------|-----------|-----------|
|                | Baseline | Day 1     | Day 2     | Day 3     |
| HR (beats per minute) | 124.0 ± 12.1 | 120.6 ± 10.3 | 122.5 ± 9.8 | 121.2 ± 8.5 |
| SBP (mmHg)      | 85.7 ± 10.9 | 83.1 ± 12.4 | 85.3 ± 11.9 | 84.4 ± 9.6 |
| DBP (mmHg)      | 52.5 ± 6.6  | 51.4 ± 7.3  | 51.7 ± 8.2  | 52.8 ± 9.0  |

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure
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Propranolol and timolol maleate, as non-selective β-adrenergic blockers, are effective in the treatment of hemangioma, but the mechanism of their action remains unknown, but some scholars presumed that the mechanism of timolol maleate is the same as for propranolol. Bingham et al. studies have shown that propranolol may antagonize β-adrenergic receptor-mediated vasodilation, leading to vasoconstriction, which may explain the volume reduction and color fading of hemangiomas caused by the application of propranolol. Fredriksson et al. have found propranolol may block angiogenesis mediated by VEGF and for that β-adrenergic receptor signaling can increase VEGF-A expression. Storch et al. have shown that propranolol may increase apoptosis. Because β-adrenergic agonists can inhibit the apoptosis of many different types of cells. The above three hypotheses are consistent with the clinical observation of propranolol in the treatment of hemangioma. Lee et al. suggested that hemPericytes expressed high levels of β2-adrenergic receptor mRNA compared with positive control bladder smooth muscle cells. In addition, β2-adrenergic receptor mRNA levels were relatively high in IH specimens compared with β1, β3 and β1b-adrenergic receptor. It is concluded that the mechanism of propranolol acting on proliferative hemangioma increases the contraction of hemangioma peripheral cells, and further points out that hemangioma peripheral cells may be a target of propranolol. The reason why very few hemangiomas are insensitive to propranolol treatment may be the low levels of β1 and β2 adrenergic receptors in these hemangioma specimens.

The combined use of drugs in the treatment of mixed hemangioma in parotid region is effective and safe. It can be used as first-line treatment of compound hemangioma selection.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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