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Evaluation of the efficacy and safety of propranolol, timolol maleate, and the combination of the two, in the treatment of superficial infantile haemangiomas

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Abstract

Our aim was to compare in a prospective study the clinical effects and safety of propranolol given orally, timolol maleate applied locally, and the combination of the two, in the management of superficial infantile haemangiomas. Thirty-nine patients with superficial infantile haemangiomas were randomised into three equal groups of 13 each: the first given timolol maleate applied topically together with propranolol given orally, the second given only propranolol orally, and the third given only timolol maleate topically. Photographs were taken before, and periodically after, starting treatment. A minimum of 50% improvement was considered to be effective. The maximum duration of treatment was planned for 6 months, and the patients were followed up for 3-12 months. The overall rate of clinical effectiveness for the three groups was 11/13, 9/13, and 8/13, respectively. The two drugs together had a shorter effective response time than when they were given separately. There were no serious adverse effects. We therefore conclude that timolol maleate given topically together with propranolol given orally is safe and effective in the treatment of superficial infantile haemangiomas. Compared with simple medication, this method is more rapid, has an appreciable effect, takes a shorter time, and has fewer adverse reactions. It could be used as a first-line treatment, particularly if the lesion is potentially disfiguring or functionally threatening such as large periocular superficial haemangiomas.

Keywords: Infantile haemangiomas; Timolol maleate; Propranolol

Introduction

Haemangiomas are the most common benign tumours of infancy, and affect as many as 1.2% -12% of infants younger than a year old. Up to 60% of such tumours present on the head and neck,[1] though they can also occur on the trunk and limbs. They are self-limiting, often first seen in the neonatal period, later enter the proliferative phase, and finally cease development around the age of 1 when they begin to regress. In over half of 5-year-old patients and three-quarters of 7-year-old patients they regress completely.[2]

In 2008, Léauté-Labrèze et al.[3] first reported the use of propranolol in their treatment and achieved good results. A later series of reports confirmed this. In 2010, Guo et al.[4] first reported on the use of topical treatment for haemangioma of the eyelid using a non-selective β-blocker solution, and the curative effect was obvious. Subsequently, Ye et al[5] confirmed that timolol maleate used topically is effective and safe for treating superficial haaemangiomas. We began to treat then with timolol maleate applied topically in October 2012.

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However, to our knowledge the efficacy of propranolol and timolol maleate and the effect of a single drug compared with the combination of the two drugs has not been proved. In this prospective study we compared the efficacy of propranolol, timolol maleate and the combination of the two drugs in infants with superficial haemangiomas.

Patients and methods

We studied 39 inpatients who presented with superficial infantile haemangiomas from October 2012 to August 2013 at the Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University. There were 15 boys and 24 girls, age range 2-9 months. The haemangiomas were in the eyelids, lips, nose, and ears (n=22) and parotid and cheek (n=17). The inclusion criteria were patients younger than 12 months with superficial haemangiomas who had had no previous treatment. The diagnosis was made from the medical history, presentation, ultrasound, computed, or magnetic resonance imaging, and the chest radiograph, electrocardiogram, blood glucose concentration, tests of liver and renal function, and routine blood examinations were within the reference ranges. The following were excluded: those with deep or mixed haemangiomas, bronchial asthma, pneumonia, sinus bradycardia or atrioventricular block (second degree and above), fever, and diarrhoea or respiratory infections.

A random sequence was generated using a computer program to assign patients in a 1:1:1 ratio to three groups of 13 patients each. The first (five boys and seven girls) were given propranolol orally and timolol maleate topically, the second (four boys and seven girls) were given propranolol orally, and the third (six boys and 11 girls) were given timolol maleate topically. Qin et al found no significant difference between the different primary tumour sites, so our groups were not subdivided by area.[6] The clinical study was approved by the China Medical University Review Board, and the children's parents gave signed informed consent.

Treatment

The parents of infants in the first group were instructed to apply a small amount of 0.5% timolol maleate eye drops to the lesion twice daily (25 mg/5 ml, Wuhan King Pharmaceutical Co. Ltd. Wuhan, China) with medical cotton swabs. However, the eye drops were not to be applied to the cornea or conjunctiva in children with periocular haemangiomas. Children in this group also took propranolol (10 mg tablet, Tianjin Lisheng Pharmaceutical Co. Ltd. Tianjin, China) at a 1.0 mg/kg dose orally once a day with food. The children in the second group were given propranolol (1.5 mg/kg) alone once a day with food, and the third group were given timolol maleate alone topically in the same dose as in the first group.

The infants' heart rate, blood pressure, and other vital signs were carefully monitored during treatment, and the parents were asked to monitor whether their children developed localised redness, or symptoms such as loss of appetite, nausea, vomiting, wheezing, shortness of breath, or lethargy. If they did, the parents were instructed to stop the drugs immediately and to watch their children carefully. The infants were periodically re-examined to note the size and colour of the haemangioma and assess the effect of treatment. Treatment was stopped when the lesions had regressed completely or the infant had had up to 6 months of treatment without improvement.

Evaluation of the efficacy

The efficacy of treatment was evaluated based on the clinical photographs taken at the onset of treatment and those taken during, and at the end of, treatment. The size of each lesion was measured, and the change in size before and after treatment was used to assess the outcome. A panel of three surgeons who were unaware of which treatment the infant had been given and the response rates, assessed the outcomes. The improvement in size after treatment was graded on a 4-point scale as proposed by Achauer et al[7]: class I (poor) - reduction in size of <25%; class II (moderate) - reduction in size of 25% - 50%; class III (good) - reduction in size of 50% - 75%; and class IV (excellent) - reduction in size of 75% - 100%. Classes I and II were considered ineffective treatment, and classes III and IV effective treatment.

Results

Twenty-four hours after the first treatment the tension of the surface of the tumour had decreased in most children, and the texture had become softer. Typical cases are shown in Figs. 1-6. The number of infants who responded well to treatment is shown in Table 1.

Fig. 1. Before treatment: a 2½-month-old girl with a superficial haemangioma of her nose (published with the parents' permission).