Comparison of the efficacy and safety of topical timolol and oral propranolol for the treatment of Superficial Infantile Haemangiomas

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Abstract

Background: Infantile haemangiomas (IHs) are the most common vascular tumours of infancy. In recenttime oral propranolol has achieved great success in treating IHs. To minimize the systemic side events caused by oral propranolol, topical timolol started to be applied in the treatment of IHs, especially for superficial lesions.

Methods: We treated 50 children with superficial IHs using oral propranolol on 25 patients and, topical timolol on 25 patients and investigated the efficacy and safety of the two treatment patterns.

Results: Both oral propranolol and topical timolol achieved a satisfactory therapeutic outcome, with an effective response rate of 96 and 95.4%, respectively. No significant differences in visual analogy scale (VAS) improvement between the two groups were observed. Systemic adverse events for patients treated with oral propranolol (3.9%) was significantly higher than that for patients treated with topical timolol. Clinical response was not associated with gender, duration of treatment, lesion location, lesion size, and gestational age but closely associated with age at treatment initiation, which indicated that younger age at treatment initiation predicted for a better regression rate.

Conclusion: Topical timolol could be the first-line therapy for superficial IHs because of its good efficacy and improved safety profile.

Key words: infantile haemangioma, topical timolol, oral propranolol.

Introduction

Infantile haemangiomas (IHs) are the most common vascular tumours of infancy with male to female ratio of 1:3-5[1]. It occurs in 4 to 5% of infants occurring within first few weeks of life. The cause of haemangioma is still unknown, but it is associated with the disorder of angiogenesis and vasculogenesis[2]. Most of the IHs occur as a single cutaneous lesion with predilection for head and neck followed by trunk and extremities. Owing to the characteristic growth pattern of IHs as of rapid proliferation and followed by involution, conservative therapeutic strategies without any early interference were prevalent over several decades[3]. However, observational treatment failed to achieve satisfactory therapeutic and cosmetic effects because of the slow rate of tumour regression and permanent residuals leading to cosmetic problems[4]. In 2008, Léauté-Labrèze et al[5] reported their results of successfully treating IHs with oral propranolol. Since then, propranolol had become the first-line drug for IHs, but its molecular mechanisms are not well-elucidated[6]. Furthermore, several systemic drug adverse events (AEs) have been observed in certain patients after oral propranolol[7]. To minimize potential side effects caused by systemic use of propranolol, topical timolol started to be applied in the treatment of IHs, especially for superficial lesions[8-11]. In the present study, we studied patients with superficial IHs treated either with topical timolol or oral propranolol, and aimed to compare the efficacy and safety of two treatment patterns.

Materials And Methods

The study protocol was done in accordance with Declaration of Helsinki, and informed consents were obtained from the guardians of all the patients. The

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study was done between October 2019 and October 2021 at a tertiary care centre. Consecutive patients diagnosed as superficial IHs were collected in the present study. Total 50 patients were included in the study and based on simple randomization method they are divided in two groups. The exclusion criteria included a history of contraindications of β-blockers, other IH lesions including ulcerated, mucosal, mixed, or deep IHs.

Before the initiation of treatment, all patients had undergone thorough physical examination. Clinical features and images of superficial lesions were recorded prior to the treatment. For oral propranolol treatment, patients were given oral propranolol at a dose of 1.0 mg/kg per day. Propranolol was divided into 2 doses and taken within half hours after meals. For topical timolol treatment, timolol maleate 0.5% eye drop was applied three times a day. The eye drop was gently rubbed over the whole surface of IH. Cardiovascular examination was done before and after the first application of propranolol or timolol. The treatment continued until resolution of the lesion or no further improvement was achieved. To record systemic or local AEs, all the patients' guardians were given a questionnaire that include all potential AEs, including erythema, oedema, crusting, erosion, ulceration, local infections, asthma, bradycardia, hypotension, hypoglycaemia, peripheral vasoconstriction, gastrointestinal disturbances, behavioural changes, sleep disturbances, and diarrhoea[13]. Therapeutic responses were defined as blanching and softening of the lesions after treatment initiation. The therapeutic efficacy was mainly evaluated by using visual analogue scale (VAS)[14]. All clinical photographs of IHs before and after treatment were checked (Figure 1 & 2). The VAS score was determined by the change in the appearance, which ranges from −100 (representing a doubling in the size and extent of the IH) to 100 (representing complete resolution)[12]. The responses were graded as : excellent (VAS score ranging from 90 to 100), good (VAS score ranging from 51-90), fair (VAS score ranging from 1-50) and poor (VAS score ranging from − 100 to 0).

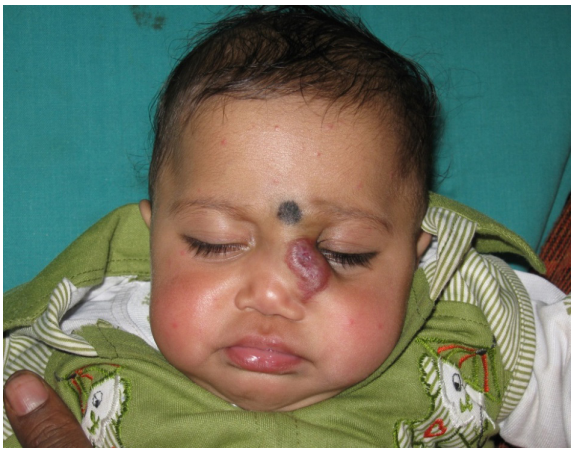

Figure 1: Pretreatment

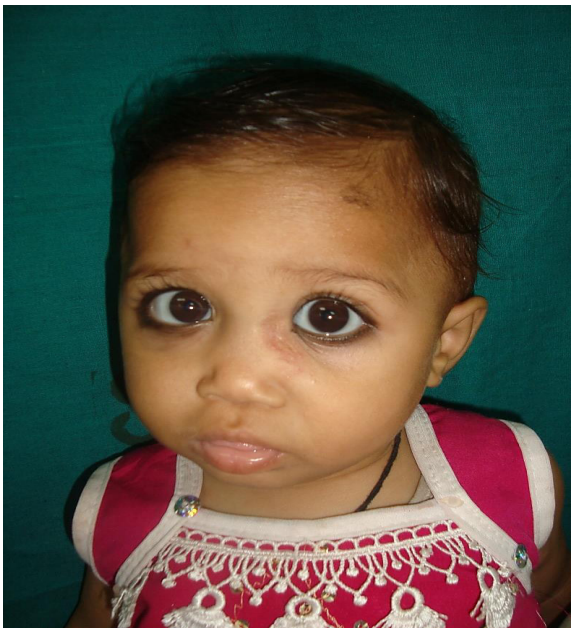

Figure 2: Post-treatment (propranolol) after 6 months

Results

The mean age at initiation of the treatment was 5.8 months. The ratio of female to male was 2.1:1 (34 females and 16 males) and 16% (8/50) of patients were born prematurely. Tumoursize ranged from 0.5 to 20.2 cm^2, with a mean size of 4.42 cm^2. The mean duration of treatment was 6.4 months.

Fifty patients were included in the study, including 25 patients treated with oral propranolol and 25 patients treated with topical timolol. No significant differences in age, location, gestational age, treatment duration, and follow-up time were observed in two groups. For patients treated with oral propranolol, the mean age at treatment initiation was 5 months. The primary locations included head and neck region excluding periocular region (26), periocular region (9), torso (7), extremities (5), and perineal region (3) (table-1). The

mean duration of oral propranolol treatment was 6.0 months, and the mean follow-up time was 6.2 months. For patients treated with topical timolol, the mean age at treatment initiation was 5.4 months. The mean duration of topical timolol treatment was 7.3 months, and the mean follow-up time was 6.5 months.

Table 1- Distribution of Infantile Haemangiomas on body.

Head and neck region excluding Periocular Region	26
Periocular region	9
torso	7
Extremity	5
Perineal region	3

Both propranolol and timolol had satisfactory outcome in treating superficial IHs, and no significant differences in VAS improvement had been observed (P = 0.20). The average VAS improvement after oral propranolol treatment was 71.2, with 13 patients achieving excellent response 7 patients achieving good response, 3 patients achieving fair response and 2 patients achieving poor response (Table-2).

Table 2- Improvement after oral propranolol treatment.

Average VAS	71.2
Excellent response	13
Good response	7
Fair response	3
Poor response	2

The average VAS improvement after topical timolol treatment was 77.2, with 15 patients had achieved excellent response, 6 patients achieved good response, 3 patients achieved fair response and 1patients achieved poor response(**Table-3**).

Table 3- Improvement after topical timolol treatment.

Average VAS	77.2
Excellent response	15
Good response	6
Fair response	3
Poor response	1

No systemic AEs had been noted during topical timolol treatment, compared with 3 patients experienced systemic AEs during oral propranolol treatment. Meanwhile, mild local side effects had been observed in 2 patients treated with topical timolol, including local pruritus.

Clinical response had not been associated with gender, duration of treatment, lesion location, lesion size, gestational age. The only predictor for clinical responses was age at which treatment was initiation for both groups, which indicated that better therapeutic effects were achieved in patients with younger age in other words less than 6 months of ages.

Therapeutic Effects for periocular IHs:

We had evaluated the therapeutic effects for peri ocular haemangiomas treated by propranolol or timolol. Total 9 patients had IHsof which 4 patients were treated with oral propranolol and 5 patients were treated by topical Timolol. Both propranolol and timolol achieved a satisfactory outcome in treating these superficial IHs, and no significant differences in therapeutic effects were observed in the present study (P = 0.52). 3patients treated by oral propranolol achieved excellent response, 1patients achieving fair response and none had poor response. In contrast, 3 patients treated by topical timolol achieved excellent response, with 2 patients achieving good response, none had poor response.

Discussion

The treatment pattern of IHs has been changed dramatically since the introduction of propranolol for the treatment of IHS. Although, common systemic side effects like hypotension, hypoglycaemia, bradycardia, bronchospasm, electrolyte disturbances and diarrhoea, are usually self-limiting without any special intervention[15], concerns regarding the potential effects of propranolol on neurocognitive ability have been raised very recently. It is well known that the lipophilic nature of propranolol could favour in penetrating the blood-brain barrier, but whether oral propranolol would affect the central nervous system over long period is still unclear[16]. As for the superficial lesions, topical medication could have achieved local drug distribution and reduce the amount of the drug into blood circulation. Although topical beta blockers have achieved acceptance for the treatment of superficial IHs, there is still no consensus on the selection of oral propranolol or topical timolol for treating superficial IHs. Fewer systemic adverse effect had been observed in patients receiving topical timolol than those receiving oral propranolol. This study had provided some supportive evidence in choosing topical timolol as the first-line therapy for superficial IHs. Propranolol, as a non-selective β-blocker, could suppress the growth of IHs through inducing vasoconstriction, angiogenesis inhibition, and apoptosis induction[17]. Propranolol had been proved to be a good choice for the treatment of obstructive, alarming and ulcerated haemangiomas[1]. In the present study, we applied propranolol at a dosage of 1 mg/kg per day, with an effective response rate

of 96%, which is consistent with the results (94-98%) by Léauté-Labrèze et al[1]. Propranolol and timolol are both β-blockers, which may regulate the growth of IHs via same mechanism. However, few studies had been conducted to compare the therapeutic effects of topical timolol and oral propranolol. Our results had shown no significant differences in efficacy between the two treatment modalities, and both treatments could be adopted for superficial IHs. To reduce systemic side effects caused by oral propranolol is one of the main reason for applying topical timolol as an alternative of treating IHs, but only a few studies had investigated the improvement of treatment safety by comparing the outcomes of patients treated with either oral propranolol or topical timolol. Our study had shown only fewer systemic AEs in patients receiving topical timolol than those receiving oral propranolol. Of the 50 children in the propranolol group, 3 patients had systemic adverse reactions, including 2 with sleep disorders, 1 with loss of appetite. Compared with the propranolol group, 50 patients in the timolol group had no systemic adverse drug reactions and only 2 patients had local side effects. These shows that the occurrence of systemic AEs for patients treated with oral propranolol were significantly higher than that for the patients treated with topical timolol ($P > 0.05$). Therefore, we recommend topical timolol instead of oral propranolol as the first-line therapy for the superficial IHs because of its good efficacy and improved safety profile. As it had been shown in the results, age at treatment initiation was closely associated with the therapeutic efficacy in both groups, with a higher improvement rate for patients younger than 6 months old treated with either topical timolol or oral propranolol. These results were consistent with previous studies, which had shown better regression rate of IHs lesions achieved in patients younger than 6 months[10,18]. We hypothesized that this phenomenon was due to the characteristic growth behaviour of IHs. A rapid proliferation and followed regression is the typical distinct feature of IH. Rapid growth of superficial IHs lesions are usually observed during first 5-8 weeks and about 80% of their total growth were completed by the age of 3 months[19-20]. It is widely accepted that rapid proliferation and followed regression of IH lesions are closely associated with the crucial role of beta adrenergic receptors[21]. The β-blockers like propranolol and timolol could have elicit inhibitory effects via regulating the cell proliferation, angiogenesis and apoptosis through beta adrenergic receptor signalling pathway. It is widely accepted that dysregulated differentiation of embryonic cells could have contributed to the progression of IHs, which is composed of proliferative haemangioma endothelial cells as well as immature haemangioma pericytes circumscribeing the vessels[22,23]. According to the recent studies on the potential mechanisms of different antihemangioma drugs beta-blockers mainly exert their effects via targeting haemangioma endothelial cells and haemangioma pericytes[24]. Bischoff et al proposed that the propranolol could suppress the development of haemangiomas through increasing the contractility of haemangioma pericytes[25], and several other studies reported that the propranolol could inhibit the growth of haemangiomas via modulating cellular functions of haemangioma endothelial cells[26]. Although no significant differences in the therapeutic efficacy of oral propranolol or topical timolol were observed. It is possible that systemic propranolol had been dissolved in the blood and firstly affected cellular physiology of haemangioma endothelial cells across the vessels, while topical timolol passes through the skin and firstly act on haemangioma pericytes circumscribing the vessels. As a result, systemic propranolol might mainly target endothelial cells initially, and topical timolol might mainly target pericytes initially. However, few evidences provide support for our hypothesis. Therefore, more studies are needed to compare the potential mechanisms of local and systemic beta-blockers on treating haemangiomas.

Conclusion

In the present study, we discovered that topical timolol is as effective as oral propranolol for the treatment of superficial IHs, and had less risk for systemic adverse events. Therefore, we recommend topical timolol as the first-line therapy for superficial IHs.

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Conflict of interest: Nil
Source of funding: Nil

Date received: Nov 25, 2021
Date accepted: May 12, 2022