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Topical application of timolol decreases the severity and frequency of epistaxis in patients who have previously undergone nasal dermoplasty for hereditary hemorrhagic telangiectasia

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ABSTRACT

Objective: Hereditary hemorrhagic telangiectasia (HHT) is widely known to cause bleeding that is difficult to control because of the associated vascular wall fragility. Although nasal dermoplasty results in decreased severity and frequency of nasal bleeding in patients with HHT, it does not eradicate epistaxis because this procedure cannot cover the entire nasal cavity. Residual bleeding warrants additional effective therapy. Preliminary reports on the use of β-adrenergic blockers for treating epistaxis in patients with HHT encouraged us to examine their effects in HHT patients who had previously undergone nasal dermoplasty but still complained of epistaxis.
Methods: We performed a prospective topical timolol, a nonselective beta blocker, application study involving 12 HHT patients who had undergone nasal dermoplasty. The observation period lasted for 3 months.
Results: There was one improperly enrolled case in which timolol administration was discontinued. The mean score of bleeding intensity and that of bleeding frequency were markedly reduced after treatment. Two patients who had required transfusions before treatment did not need them afterward, and patients were generally satisfied with the treatment.
Conclusion: Topical timolol application was effective in decreasing epistaxis. Although no adverse effects were observed in the properly selected patients, there are contraindications to timolol application that should be kept in mind when applying this treatment.

1. Introduction

Many physicians who have treated a patient with hereditary hemorrhagic telangiectasia (HHT) have experienced difficulty in controlling bleeding because of the associated vascular wall fragility. In these patients, slight trauma may result in profuse bleeding because no effective contraction or retraction mechanisms are in place to control the hemorrhage. As a result, routine first aid measures such as packing the nose may exacerbate the situation by causing further trauma to the vessels. Therefore, treatment options should be selected with consideration of the bleeding mechanism. Currently, surgical nostril closure is regarded as the best treatment, but this procedure is not necessarily accepted by every patient. Nasal dermoplasty (ND) is considered the second-best option. This procedure results in decreased severity and frequency of bleeding. Unfortunately, although ND decreases bleeding, it does not eradicate epistaxis because this procedure is confined to the anterior portion of the nasal cavity; postoperative local graft failure can also occur. Patients who improve after the treatment are likely to request further improvement. This situation equally applies to patients with HHT. If persistent epistaxis bothers patients, physicians and patients are likely to hesitate in pursuing additional surgery and

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may instead turn to powerful medication to control bleeding. Bevacizumab [1] and thalidomide [2] have been reported to be promising medical treatments. However, we are rather reluctant to use these medications because of economic issues and adverse effects, so we sought a novel drug that would be easy and safe to use.

The efficacy of propranolol, a β-adrenergic blocker, in treating various vascular diseases has been recently reported. Strong evidence of efficacy has been obtained, particularly in cases of infantile hemangioma [3]. Propranolol is thought to be a promising treatment for HHT; it results in elevated TGF-β signaling or in angiogenesis inhibition that may reduce pathological endothelial cell activation in HHT lesions. Although the systemic administration of propranolol has been reported to cause increased epistaxis, the possibility of using it topically to reduce epistaxis has been raised [4]. A case report on the topical application of timolol, another β-adrenergic blocker, was published in 2012 [5], and a significant reduction in the frequency and severity of epistaxis was noted. Although we do not have any beta blockers as topical nasal preparations, we have already had timolol solution as an ophthalmic drop and such a preparation can be used as a nasal drop. We sought to verify this inhibitory effect of timolol on epistaxis in HHT patients who had previously undergone ND.

2. Materials and methods

Patients who had undergone nasal dermoplasty but still complained of epistaxis after surgery were enrolled in this study. Case exclusion criteria are shown in Table 1. This study was approved by the clinical study ethical review board of Jichi Medical University.

Timolol ophthalmic solution (0.5%) was applied as a nasal drop into each nostril 3 times daily. Patients received biweekly follow-up to evaluate efficacy and adverse effects. The observation period lasted for 3 months. Regular medications were continued, but the introduction of new drugs that could affect the study was prohibited. Efficacy was evaluated as the main outcome using the grading system proposed by Al-Dean & Bachmann-Harildstad (Table 2). Objective nasal findings, symptoms, adverse effects, and patients' level of satisfaction were examined as secondary outcomes. Data were analyzed by using Wilcoxon's signed rank sum test. Tests with p values less than 0.05 were considered to be statistically significant.

Table 1
Case exclusion criteria.

1. Anticoagulants or aspirin intake
2. Pregnant women
3. Under 20 years old
4. Conditions wherein careful administration of timolol is necessary
Right ventricular failure due to pulmonary hypertension
Congestive heart failure
Diabetic ketoacidosis or metabolic acidosis
Uncontrolled diabetes mellitus
5. Contraindication for systemic β adrenergic blocker administration
Hypersensitivity to β blockers
Possible bronchial asthma or bronchospasm
Symptomatic or high grade following disorders; Bradycardia, 2nd or 3rd grade of atrioventricular block, sinoatrial block, sick sinus syndrome
Cardiogenic shock
Hypotension
Long lasting starvation

Table 2
Epistaxis grading system by Al-Deen and Bachmann-Harildstad.

Intensity of bleeding	
0	None
1	Slight stains on the handkerchief
2	Soaked handkerchief
3	Soaked towel
4	Bowl or similar vessel is necessary
Frequency of bleeding (during period of 4 weeks)	
0	None
1	1–5 times
2	6–10 times
3	11–29 times
4	Daily
Frequency of blood transfusion	
0	None
1	Once
2	2 or more

3. Results

Twelve patients were enrolled from May 2013 to March 2014. A 78-year-old male patient presented with disequilibrium, hypotension, and bradycardia after administration of timolol on the second day. This patient had previously undergone nasal dermoplasty, which was not judged to be contraindicated despite the presence of atrial fibrillation. He then developed heart failure and began to administer digoxin but did not declare the issue upon entry into this study. This patient should not have been a candidate and was excluded from the study. As a result, eleven patients (6 males and 5 females) completed the study; their mean age was 61.5 ± 8.3 years.

Demographic data and the results of timolol treatment are shown in Table 3. The mean score of bleeding intensity was significantly reduced from 2.09 to 1.18 ($p = 0.004$) and that of bleeding frequency was also significantly reduced from 2.91 to 1.73 ($p = 0.006$).

Before treatment, blood transfusions had been required in 2 patients. These patients did not need transfusions after the treatment.

Changes in the objective finding of vascular lesions in the nasal mucosa after treatment varied between individuals; Remarkable improvement was observed in seven cases as shown in Fig. 1, while no significant changes were recognized in other cases.

Patients' post-treatment satisfaction levels were as follows: results quite satisfactory, 4; patients somewhat satisfied, 5; rather discontented, 2; and discontented, 0. No adverse effects were reported.

4. Discussion

Nasal dermoplasty is a frequently recommended option for controlling epistaxis in HHT patients despite its lower efficacy relative to surgical nostril closure. Although the severity and frequency of epistaxis are typically dramatically lessened after ND, there can be some residual bleeding after the procedure. This is typically due to areas left uncovered and those that failed to take the grafts; engorged vessels in the skin are typically responsible for bleeding in the postoperative period.

We previously tried to introduce two maneuvers to decrease the risk of postoperative epistaxis: circumferential skin grafting (instead of grafting restricted to the septum) and the MW method for cases of septal perforation [6]. However, bleeding from the dilated vessels in the mucous membranes posterior to the grafted area and from the vestibular skin cannot be dealt with using these

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