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Good Clinical Responders to Topical Timolol in Patients with Infantile Hemangiomas: A 7-Year Retrospective Study of 328 Korean Patients

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Background: Topical timolol is widely used for treatment of superficial infantile hemangioma (IH). However, little is known about factors that affect the response to topical timolol treatment.
Objective: This study aimed to investigate the efficacy, safety, and predictive value for good response to topical timolol for IH.
Methods: A retrospective review of medical records and clinical photos of 328 patients with IH treated with topical timolol 0.5% solution was conducted. Serial clinical photographs were compared with those at the initial visit using a 100-mm visual analogue scale (VAS). Treatment response was defined as an improvement of at least 75% from baseline in IH lesions within 12 months of treatment.
Results: Overall, IH patients treated with topical timolol showed significant improvement from baseline, showing that the final VAS score within 12 months of treatment was 69.7±20.4. The multivariable logistic regression analysis showed age at initiation of treatment (p=0.007), length of gestation and fetal growth (p=0.03), depth (p=0.01), and flexural area (p=0.007) were significantly associated with treatment response. Only four patients (1.1%) reported local irritation.
Conclusion: This study demonstrated that topical timolol treatment was an effective and well-tolerated treatment for IHs. Physicians are encouraged to consider several patient- or lesional factors that might affect treatment response to achieve better clinical outcomes.

Keywords: Capillary hemangioma, Timolol, Treatment outcome, Visual analog scale

INTRODUCTION

Infantile hemangiomas (IHs) are the most common type of soft tissue tumors in infants and young children, with a prevalence of 4.5%[1,2]. Although most IHs usually regress spontaneously, treatment should be performed if they cause life-threatening events, functional impairment, and disfigurement. Long-term sequelae can result from residual changes such as epidermal atrophy, fibrofatty residuum, scar formation, and telangiectasis[3].

Therapeutic options for IHs include systemic beta-blockers, systemic or intralesional corticosteroids, surgical resection, and laser treatment; recently, oral propranolol is considered as the first-line management for IH lesions that require treatment[4]. Propranolol causes vasoconstriction of the feeding vessels, suppression or blockade of VEGF, blockade of GLUT 1 receptors, and inhibition of angiogenesis and vasculogenesis[5]. As reported in a large cohort study[6], a randomized controlled trial[7], and a meta-analysis of 1,264 reported cases[8], 96%~98% of IH lesions improved after an average of 6 months of treatment with a dose of 2~3 mg/kg per day of oral propranolol.

Although adverse events are usually self-limiting without the need for special intervention[9], the systemic side effects of oral propranolol include sleep disorders, bradycardia, hypoglycemia, and breathing problems[10]. In addition, because of its lipophilicity, propranolol has potential side effects in the central nervous system[11,12]. Therefore, contraindications, such as preterm infants, infants weighing less than 2 kg, reactive airway disease, significant cardiac disease, compromised renal function, and central nervous system disorders, limit the availability of many patients[5,13].

Topical timolol, a nonselective beta blocker, is another good treatment option, especially for superficial IHs, considering its fewer systemic effects[14,15]. Timolol maleate is 8 times more potent than propranolol as a beta blocker, and its lipophilic nature can enhance transcutaneous penetration[16]. A randomized placebo-controlled trial in infants aged 5~24 weeks reported that treatment with topical timolol 0.5% gel for 24 weeks is a safe and effective therapy for patients with superficial IH[17]. A recent systematic review and meta-analysis revealed that treatment with topical timolol showed significantly higher improvement from baseline compared with untreated control groups with a relative risk 8.86 (95% confidence interval [CI], 5.07~15.47)[18]. Additionally, topical timolol treatment did not significantly differ from systemic propranolol treatment when comparing the response rate[19-21].

Although its efficacy and safety have been studied in several studies, there is still a lack of research on which factors are good predictors of clinical response to topical timolol treatment. Inconsistent data have been reported on the factors related to clinical response, such as age at treatment initiation, gender, treatment duration, gestational age, lesion size, depth, or location[22-25]. Therefore, we reviewed our tertiary institutional experience with the use of topical timolol for the treatment of IH. We aimed to investigate the clinical outcomes of topical timolol and identify several factors affecting the treatment response.

MATERIALS AND METHODS

Study design and population

We retrospectively reviewed the medical records and clinical images of patients with IH treated with topical timolol at Seoul National University Hospital between June 2011 and December 2017. Patients who were treated with topical timolol monotherapy were included. Patients were instructed to apply one drop of timolol solution 0.5% (Rysmon TG ophthalmic solution 0.5%; Hanmi Pharmaceutical, Seoul, Korea or Timoptic XE ophthalmic solution 0.5%; Santen Pharmaceutical, Osaka, Japan) twice daily on IH lesions. Patients treated with topical timolol were followed regularly at 1 month after the baseline visit and every 1~3 months thereafter. Clinical photographs of IH patients were taken at every visit. Patients treated with combination therapy or other therapeutic agents, such as systemic propranolol, systemic steroids, intralesional steroid injections, topical corticosteroids, were excluded. Patients who were diagnosed with other vascular tumors or vascular malformations, patients without good quality photographic records, or patients who were lost to follow-up were also excluded.

This study was reviewed and approved by the Institutional Review Board of the Seoul National University Hospital (approval no. #H-1809-053-971), and the requirement for informed consent was waived. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Evaluation of infantile hemangiomas and definition of visual analogue scale score

Three investigators (DAY, JSP, and HL) independently evaluated all clinical photographs, compared every follow-up visit image against baseline visit. The investigators were asked to assess improvement of each lesion in the overall respect of decrease in size and blanching of color by the visual analogue scale (VAS) score from –100 to +100. The VAS is a 100-mm scale and is rated as follows: +100 indicate complete resolution of the lesion, 0 indicates no change, and –100 indicates doubling of size or color compared with that of the initial visit[24]. A negative value of the VAS score represented worsening of the lesion, and a positive value represented improvement. If the investigator assessed a 50% reduction in size or color of the lesion compared to the baseline visit, a VAS score of +50 was scored. After scoring each clinical images, the mean VAS score between each investigator was used for analysis. The Krippendorff's alpha coefficient was used to measure the agreement among the three investigators.

VAS_N was defined as the VAS score at N months from baseline. Months were calculated by rounding up to the nearest month from the baseline visit. The final VAS score was defined as the VAS score at the last visit during the first 12 months of treatment, considering that the follow-up intervals were different for each patient and treatment could be terminated early with almost complete clearance within a few months. Treatment response was defined as an improvement

of at least 75% from baseline in IH lesions within 12 months of treatment.

Patients' characteristics, lesion characteristics, and adverse events

Medical charts were reviewed to determine patient and lesion characteristics. Patient information included age, sex, perinatal problems, family medical history, and age at initiation of treatment. Abnormalities in the length of gestation or fetal growth were recorded as perinatal problems.

Lesional factors included the number of lesions, location, depth, distribution, and complications associated with IH. Locations were categorized as head and neck, trunk, upper extremities, lower extremities, axilla, groin, and anogenital areas. The flexural area included the neck, axilla, groin, and anogenital areas. Depth was classified as superficial, deep, or mixed. The deep type was defined as a deep bluish lesion with indistinct borders, while the mixed type was defined as the presence of both deep and superficial lesions (Supplementary Fig. 1). We received the patient's consent form about publishing all photographic materials. Distributions were classified into localized, segmental, and indeterminate types. Multiple lesions were defined as the presence of two or more lesions in one patient.

Adverse events during treatment, including ulcers, bleeding, infection, and local irritation, were also reviewed.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$. Descriptive data were expressed as numbers and mean values±standard deviation. Student's t-test with Bonferroni correction was used for continuous variables. Linear mixed models were used to assess differences according to patient or lesion factors in the improvement of the VAS score[26-28]. To assess the effect over time, time and time × factor were specified as fixed factors[29,30]. To evaluate associations between predictive factors and treatment response, logistic regression analyses were performed. Predictive factors showing a univariable association ($p<0.20$) were included in the multivariable logistic regression model[31]. The graphs were plotted using Prism 5.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Patients' demographics and clinical features

In total, we identified 630 IH patients treated with topical

Table 1. Baseline demographic and clinical characteristics

Variable	Number (%)
Patient (n)	328
Sex	
Male	104 (31.7)
Female	224 (68.3)
Age at initiation of treatment (mo)	
<6	237 (72.3)
6~12	78 (23.8)
≥12	13 (4.0)
Mean±standard deviation	4.85±5.67
Presentation	
Single lesion	292 (89.0)
Multiple lesions	36 (11.0)
Multiple birth/Perinatal problems	
Twins	11 (3.4)
Preterm/SGA	22 (6.7)
Infantile hemangioma lesions (n)	382
Anatomical location	
Head and neck	176 (46.1)
Trunk	81 (21.2)
Upper extremities	66 (17.3)
Lower extremities	38 (9.9)
Axilla, inguinal, or anogenital	21 (5.5)
Depth	
Superficial	295 (77.2)
Deep	27 (7.1)
Mixed	60 (15.7)
Flexural area	
Flexural	57 (14.9)
Non-flexural	325 (85.1)
Distribution	
Localized	309 (80.9)
Segmental	55 (14.4)
Indeterminate	18 (4.7)
Complication	
Ulcerative or crusted lesions	7 (1.8)
Local irritation	4 (1.1)

SGA: small for gestational age.

timolol between June 2011 and December 2017. Patients who were lost to follow-up or were treated with other topical or systemic agents were excluded (n=302). Ultimately, 328 patients and 382 IH lesions were included in this study (Table 1). The study population was predominantly female (2.15:1 ratio). A majority of patients (n=237 [72.3%]) started treatment before the age of 6 months, and the mean age at initiation of treatment was 4.85±5.67 months. Most patients had a single lesion (n=292 [89.0%]), and only 36 (11.0%) patients had multiple lesions.

Among the 382 IH lesions, the head and neck were the most commonly involved areas (n=176 [46.1%]). With regard to the depth of IH, superficial type was the most common (295 [77.2%]) followed by the mixed type (60 [15.7%]), and deep type (27 [7.1%]). Over 309 (80.9%) patients had localized IHs, 55 (14.4%) had segmental type, and 18 (4.7%) had indeterminate type. With regard to the complications associated with IH, 7 (1.8%) lesions showed skin ulceration or crusts. Adverse events associated with topical timolol treatment such as mild local irritation was observed in

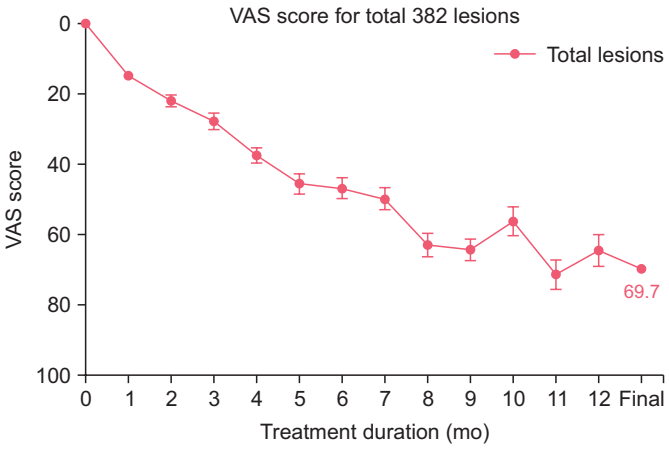
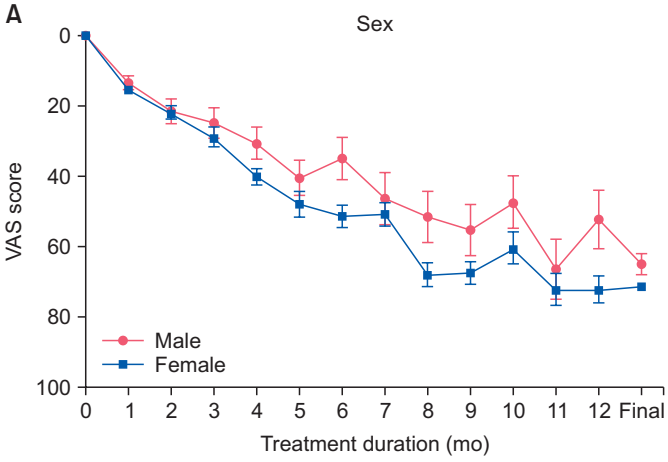
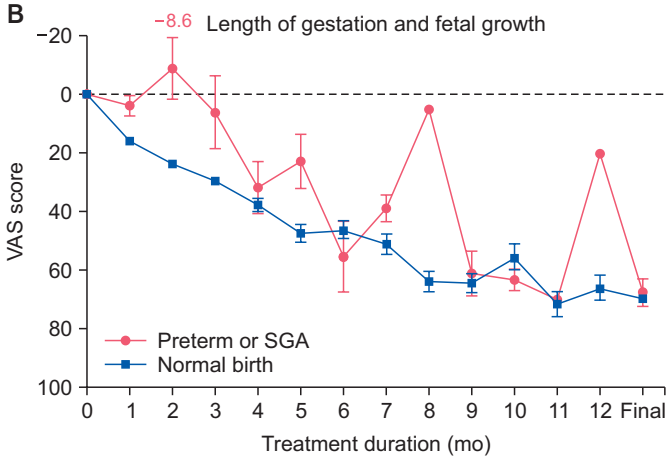


Fig. 1. Visual analogue scale (VAS) score of total patients with infantile hemangiomas treated with topical timolol.





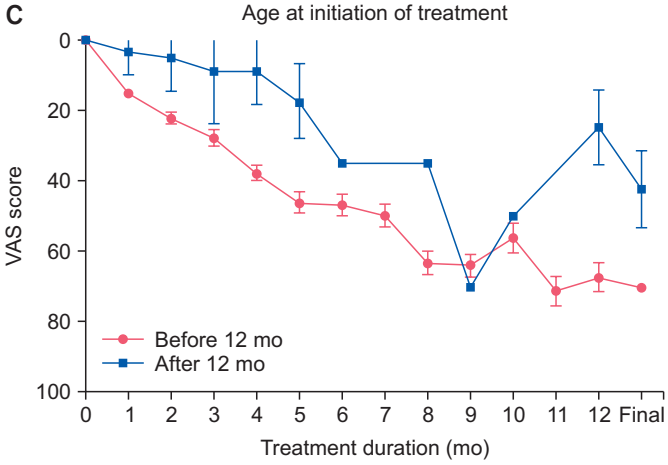


Fig. 2. Visual analogue scale (VAS) score according to patients' characteristics. (A) Infantile hemangioma lesions treated with topical timolol showed significantly higher levels of improvement over time in female patients. (B) Compared with normal-born babies, preterm or small for gestational age (SGA) infants showed significantly lower improvement at initial treatment, showing even negative mean values during treatment. (C) Patients who started treatment before 12 months of age reported a significantly higher VAS score over time.

four (1.1%) patients, whereas none had syste`mic adverse events.

Treatment outcomes and predictive factors for good response to topical timolol

Fig. 1 shows the monthly VAS scores for total IH lesions. The VAS score for 382 lesions increased gradually each month from baseline, and the final VAS score within 12 months of treatment was 69.7±20.4. Krippendorff's alpha coefficient for inter-rater reliability of the VAS scores was 0.846.

Graphical demonstration of VAS score over time was shown depending on the patients' characteristics (Fig. 2) and lesional factors (Fig. 3). Table 2 shows results of the linear mixed-model analysis. IH lesions treated with topical timolol showed significantly higher levels of improvement over time in female patients (t=3.14, p=0.002). Patients who started treatment before 12 months of age reported a significantly higher VAS score over time (t=2.91, p=0.004). Regarding lesion characteristics, superficial type (t=3.45, p=0.001), head and neck lesions (t=2.50, p=0.01), and non-flexural lesions (t=2.00, p=0.046) reported significantly higher levels of improvement over time.

To assess the initial treatment outcomes according to patient characteristics, VAS_1 and VAS_2 scores were analyzed (Supplementary Table 1). Compared with normal-born babies, preterm or small for gestational age (SGA) infants showed significantly lower improvement at initial treatment, showing even negative mean values during treatment (VAS_2 –8.6 vs. 23.8, p=0.016). As for the lesional factors (Supplementary Table 2), the head and neck lesions showed rapid improvement with topical timolol treatment compared with those in other areas (p<0.001 and 0.010 for VAS_1 and VAS_2, respectively).

A total of 115 lesions (30.1%) showed treatment response, defined as at least 75% improvement from baseline within 12 months of treatment. As shown in Table 3, the multivariable logistic regression analysis showed age at initiation of treatment (p=0.007), length of gestation and fetal growth (p=0.03), depth (p=0.01), and flexural area (p=0.007) were significantly associ-

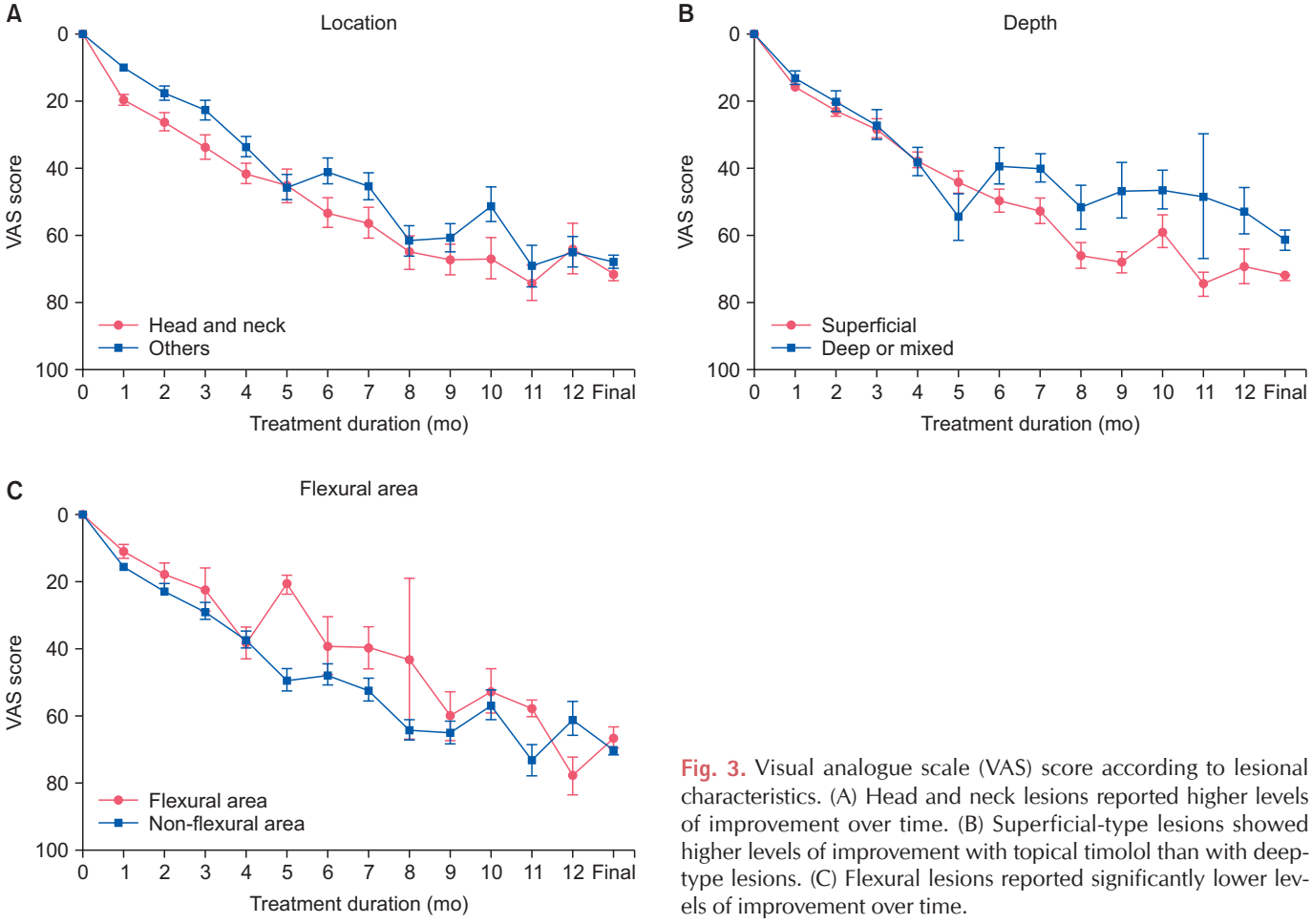


Fig. 3. Visual analogue scale (VAS) score according to lesional characteristics. (A) Head and neck lesions reported higher levels of improvement over time. (B) Superficial-type lesions showed higher levels of improvement with topical timolol than with deep-type lesions. (C) Flexural lesions reported significantly lower levels of improvement over time.

Table 2. Linear mixed model of factors associated with changes in VAS over time

Variable	Unstandardized coefficient (95% CI)	t value	*p*-value
Sex			
Female	−0.84 (−6.28 to 4.60)	−0.30	0.762
Female×time†	1.29 (0.48 to 2.10)	3.14	0.002**
Perinatal events			
Preterm or SGA	−3.17 (−12.74 to 6.40)	−0.65	0.516
Preterm or SGA×time†	−1.08 (−2.57 to 0.41)	−1.42	0.155
Age at initiation of treatment			
<12 month	0.18 (−13.51 to 13.86)	0.03	0.980
<12 month×time†	3.17 (1.03 to 5.30)	2.91	0.004**
Depth			
Superficial	−1.96 (−7.85 to 3.93)	−0.65	0.514
Superficial×time†	1.56 (0.67 to 2.44)	3.45	0.001**
Location			
H&N	1.63 (−3.33 to 6.59)	0.65	0.519
H&N x time†	0.94 (0.20 to 1.67)	2.50	0.01*
Distribution			
Non-flexural	0.92 (−6.04 to 7.88)	0.26	0.795
Non-flexural×time†	1.08 (0.02 to 2.14)	2.00	0.046*

VAS: visual analogue scale, CI: confidence interval, SGA: small for gestational age, H&N: head and neck. Statistically significant (*$p<0.05$, **$p<0.01$). †To assess the changes in VAS over time, a linear mixed effects model using analysis of covariance with the fixed factor×time was performed.

ated with treatment response. Later age at initiation of treatment (odds ratio [OR] per one month-increase 0.884; 95% CI, 0.808~0.966, per one month-increase), preterm or SGA patients (OR, 0.295; 95% CI, 0.098~0.888), and flexural area (OR, 0.349; 95% CI, 0.162~0.749) were significantly associated with no treatment response. In addition, superficial type (OR, 2.278; 95% CI, 1.216~4.269) revealed higher treatment response compared with deep of mixed type. However, sex and lesion location were no longer associated with treatment response after adjusting covariates.

DISCUSSION

This study investigated the treatment outcomes and predictive factors for clinical response to topical timolol in a large number of patients with IH. The IH lesions showed gradual improvement after topical timolol treatment, resulting in approximately 70% improvement from baseline within 12 months. Several factors, including age at initiation of treatment, length of gestation and fetal growth, depth, and flexural area resulted in differences in treatment response.

Topical timolol has been proposed as a new treatment option due to concerns over systemic side effects of oral beta-blockers. Topical timolol inhibits growth and promotes regression of superficial IH[14]. In this study, the mean value of the final VAS score was 69.7, within 12 months of treatment with timolol 0.5% solution, which indicates a significant reduction in size and color. This treatment outcome is comparable to that of systemic propranolol, resulting in an 83.8% improvement at 53 weeks after treatment[32]. Considering the possible systemic effects of oral propranolol, topical timolol can be a good treatment option that can be applied simply without requiring special work-ups or monitoring.

Inconsistent results have been reported as to whether early initiation of treatment affects treatment response. A prospective study reported the predictors for clinical responses using spectral Doppler ultrasound. The only predictor for clinical responses was age at treatment initiation; better therapeutic effects were achieved in younger patients (<6 months old)[24]. Contrarily, a recent RCT revealed that topical timolol treatment was not effective for the treatment of early proliferative

Table 3. Univariable and multivariable analysis of treatment response to topical timolol in infantile hemangiomas (n=382)

Variable	Univariable analysis				Multivariable analysis	
	Response (n=115)*	Non-response (n=267)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at initiation of treatment	3 (2~5)	4 (2~7)	0.874 (0.801~0.953)	0.002	0.884 (0.808~0.966)	0.007
Sex						
Female	87 (75.7)	183 (68.5)	Reference		–	
Male	28 (24.3)	84 (31.5)	0.701 (0.426~1.154)	0.161	–	
Length of gestation and fetal growth						
Normal birth	111 (96.5)	243 (91.0)	Reference		Reference	
Preterm or SGA	4 (3.5)	24 (9.0)	0.365 (0.124~1.077)	0.058	0.295 (0.098~0.888)	0.03
Anatomical location						
Others	58 (50.4)	148 (55.4)	Reference		–	
Head and neck	57 (49.6)	119 (44.6)	1.222 (0.789~1.894)	0.369	–	
Depth						
Deep or mixed	15 (13.0)	72 (27.0)	Reference		Reference	
Superficial	100 (87.0)	195 (73.0)	2.262 (1.342~4.513)	0.003	2.278 (1.216~4.269)	0.01
Flexural area						
Non-flexural	106 (92.2)	219 (82.0)	Reference		Reference	
Flexural	9 (7.8)	48 (18.0)	0.387 (0.183~0.819)	0.011	0.349 (0.162~0.749)	0.007

Values are presented as median (interquartile range) or number (%). OR: odds ratio, CI: confidence interval, SGA: small for gestational age. *Treatment response was defined as an improvement of at least 75% from baseline in infantile hemangioma lesions within 12 months of treatment.

IHs (<60 days old) compared with placebo[25], but the study was limited by the small number of patients included in the analysis. Our data showed older age at initiation of treatment was significantly associated with failure to achieve treatment response within 12 months after adjusting covariates (OR per one month-increase 0.884, p=0.007). Therefore, our study supports the benefits of early initiation of treatment.

Compared to normal-born babies, preterm or SGA infants had a delayed response to topical timolol, even showing a worsening course from baseline (mean VAS_2=−8.6). These findings are in line with the fact that preterm birth and low birth weight are important risk factors for IH[33,34]. Although preterm or SGA patients showed lower treatment response (OR, 0.295; p=0.03), the degree of improvement over time was not significantly different from that of normal-born babies (p=0.155). Therefore, physicians should be aware that the clinical response may begin slowly in preterm or SGA babies.

Superficial-type lesions showed higher levels of improvement with topical timolol than with deep-type lesions. This result is consistent with those of previous studies, which claimed that superficial IH lesions have a good prognosis[17,24]. Considering that topical timolol directly acts on the IH lesion through transcutaneous absorption, it seems reasonable that topical timolol is more effective in patients with superficial lesions.

The location of the hemangioma also affected the treatment outcome. Our results revealed that non-flexural area was associated with good treatment response. In addition, the head and neck area showed good initial response, but the treatment response did not show significant difference compared with other areas. This result is contradictory to the findings of a previous study, which reported that lesions in the torso were associated with a better clinical response to topical timolol[22]. Although further studies are needed to prove these contradictory findings, skin characteristics, such as thickness and elasticity, which are different for each anatomic location, may have a complex effect on the treatment outcome[35].

Adverse events of topical timolol treatment were rarely reported in this study; only four patients experienced minor

local irritation. Local irritation is a well-known side effect, accounting for nearly half of the adverse events associated with topical timolol treatment, occurring in approximately 1.64% of patients[36]. Mild itching sensation or scaly patches due to local irritation were mostly tolerable and treatment was rarely discontinued. Although some topically applied timolol is systemically absorbed in a high percentage of children[37,38], its systemic effect is thought to be insignificant compared with that of oral propranolol.

This study provides a new perspective on the factors associated with a good response to treatment with topical timolol. However, this study had some limitations. First, it was a retrospective study that did not include a control group; hence, it was not possible to distinguish the effect of topical timolol treatment from that of spontaneous regression of hemangiomas[22]. Second, the exclusion criteria probably led to selection bias, affecting the generalizability of the results. Most patients with deep or complicated IHs were treated with oral propranolol upon admission to our institution. Third, although other studies have used the VAS score to determine treatment response, it has not been strictly validated. To compensate for this limitation, two or more independent investigators evaluated and coordinated the discrepancies. Fourth, our study lacked detailed information on the systemic side effects. Laboratory examinations, including blood sugar measurement, electrocardiography, or blood pressure monitoring, were not routinely performed.

In conclusion, we propose that topical timolol is beneficial and tolerable for IH treatment. Early initiation of treatment, normal-born babies, superficial type, and non-flexural lesions were good responders to topical timolol treatment. When initiating treatment or evaluating treatment response, physicians are encouraged to consider several patient- or lesional factors to achieve better treatment outcomes. Larger-scale prospective studies with control groups are needed to confirm our findings.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-21-203-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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