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Original article

ORAL TOPICAL TIMOLOL MALEAT OR ORAL PROPRANOLOL TREATMENT FOR INFANTILE HEMANGIOMAS: CLINICAL ANALYSIS OF 403 PATIENTS

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Abstract: **Objective:** Infantile hemangiomas (IH) are the most common benign vascular tumors of infancy. Propranolol (P), a nonselective beta-blocker, has been successfully used in managing IHs. Ongoing studies investigate the efficacy of the topical β-antagonist timolol maleate (TM) in IHs. The aim of this study is to assess the effects of interventions for managing infantile hemangiomas in children.

Material and Methods: We retrospectively reviewed a total of 403 IH patients from March 2021 to March 2022. The patients were stratified into three groups. Patients in Group 1 were given TM at a dose of one drop topically twice a day, 0.5%. Patients in Group 2 were given P at a dose of 1 mg/kg twice a day. The patients in Group 3 did not receive any treatment, and observation was conducted solely by contacting the controls.

Results: The median age of diagnosis was 5 months (range 0-60), with 57.1% of the cases being male. While TM treatment was applied to 32% of the children and P treatment was applied to 46.9% of the children, no treatment was administered in 21.1%. The most common location of hemangiomas was the face, accounting for 39.2%. Hemangiomas were observed in more than one location in 48 (12%) children. The median follow-up period for the patients was 4 months (range 0-28). Hemangiomas remained unchanged in 28.3% of all cases, shrank in 60.3%, and continued to grow in 11.4%. The primary indication for initiating TM was superficial hemangiomas and infants younger than 6 months. The leading reason for starting P significantly higher than in the other groups (p : 0.001). No statistically significant differences were observed between the groups regarding bleeding and ulceration rates ($p > 0.05$).

Conclusion: The efficacy of propranolol in treating IH was higher than that of TM.

Keywords: timolol maleate, infantile hemangioma, propranolol.

INTRODUCTION

Infantile hemangiomas (IH) are proliferative hamartomas that originate from the vascular endothelium, representing the most prevalent benign tumors of childhood (1, 2, 3). Their incidence varies between 4-12% (3, 4). The assumed cell of origin for Ihs is progenitor endothelial cells originating from the chorionic villi of the placenta. Factors like the glucose transporter protein, particularly expressed by chorionic villi, and the inappropriate distribution of chorionic villus cells during fetal development have been implicated in IH development (5 ,6). Vascular endothelial growth factor A, associated with angiogenesis, is considered a primary driver of IH proliferation and contributes to treatment responses involving corticosteroids and P (7). Moreover, although rare, genetic factors might play a role in the pathogenesis of IHs (8).

IHs typically emerge in the first few weeks of life, with the most rapid growth occurring in the second postnatal month (9, 10). Growth continues until 12 months of age, after which it slows down in parallel with the child's general growth (7, 9). Approximately half of IH cases experience complete involution

by the age of 5, with 70% disappearing by age 7 and 95% regressing between ages 10 to 12 (11). However, complications such as ulceration, bleeding, functional impairment, and cosmetic issues may arise in about a quarter of cases (7). Various treatment methods have been employed, ranging from corticosteroids to propranolol, and from surgical interventions to sirolimus (12 ,13).

Presently, oral P is the preferred first-line treatment option (2, 14). It's the sole treatment for IH endorsed by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (15, 16). Although the precise mechanism of action remains uncertain, it's believed that P acts by inhibiting vasoconstriction and angiogenesis in endothelial cells, leading to apoptosis (15). Additionally, recent studies have indicated that P hinders the differentiation of hemangioma stem cells into hemangioma endothelial cells (17). Most cases experience complete resolution, with response rates reaching up to 100% (15, 18). Nonetheless, adverse effects such as hypoglycemia, bradycardia, and hypotension have been associated with propranolol (19).

However, considering the unfavorable side effects of propranolol, topical timolol maleate has also been attempted as a treatment (20).

Timolol maleate is a non-selective beta-adrenergic receptor antagonist. It may prove beneficial for treating thin, superficial Ihs (15, 16). Studies have revealed noteworthy response rates, leading to a reduction in both IH color and size (21). Nevertheless, a recent study indicated no substantial effect when using timolol for IH treatment during the early proliferative phase (16). In a cohort study, it was documented that only two patients experienced apnea or bradycardia, necessitating the discontinuation of timolol. Notably, these two patients had a history of symptomatic bradycardia prior to using the medication (22).

The primary goal of this study was to determine the most effective treatment approach for IH management.

MATERIAL AND METHODS

Pediatric patients diagnosed with infantile hemangioma, aged between 3-82 months, at a single Pediatric Oncology Clinic between 01 .03. 2021 and 01. 03. 2022 were included. Demographic and clinical data of the patients were retrospectively obtained from patient records. The patients were categorized into three groups. Patients in Group 1 were administered TM 0.5% solution at a dose of one drop topically twice a day (22). Patients in Group 2 were given P at a dose of 1 mg/kg twice a day (23). The patients in Group 3 did not receive any treatment, and observation was conducted solely by contacting the controls. In the study, a reduction of 50% or more in the size of the hemangioma after treatment was considered a reduction. Echocardiography was conducted prior to treatment due to the arrhythmia side effect of P (16, 21). Abdominal and transfontanel USG were requested to evaluate the extent of the hemangioma.

The study was approved by the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Number: 2021.12.274).

Statistical analysis

Data were analyzed using IBM SPSS, version 23 (IBM Inc., Armonk, NY, USA). Through the Kolmogorov-Smirnov test, it was determined that parameters did not exhibit normal distribution. The Kruskal-Wallis test was employed to compare parameters among groups. Dunn's test was used to identify the group responsible for the differences. The Mann-Whitney U test was utilized to compare parameters between the two groups. The Chi-square test and Fisher Freeman Halton Exact Chi-square test were applied to compare qualitative data. Statistical significance was considered when $p < 0.005$.

RESULTS

A total cohort size of 403 patients was identified, with 57.1% of the cases being male. The median age was 24 months (range 3-82) (Table 1). The median age at diagnosis was 5 months (range 0-60). While TM treatment was administered to 32% of the children and P treatment was given to 46.9% of the children, no treatment was administered in 21.1% of cases. The most common location of hemangiomas was the face, accounting for 39.2%. Other sites of occurrence are indicated in Table 2. Hemangiomas were observed in more than one location in 48 (12%) children (Table 1).

The median follow-up period was 4 months (range 0-28). The median age at the onset of treatment was 6 months (1-53 months). Hemangioma remained unchanged in 28.3% of all cases, shrank in 60.3%, and continued to grow in 11.4% (Table 2). Timolol maleate and P were administered to 129 and 189 patients, respectively. The most common indication for initiating TM was superficial hemangiomas and infants younger than 6 months (Table 2). The leading indication for starting P was facial hemangiomas (Table 2). Bleeding occurred in 1.5% of hemangioma cases, and ulceration was observed in 3.7% (Table 2). Some of the patients underwent ultrasonography and echocardiography, and the results are summarized in Table 2.

Table1. *General characteristics of the patients*

	n	Median age (months)
Age (months)	403	24 (3-82)
Age of diagnosis (months)	403	5 (0-60)
		n (%)
Group 1 Group 2 Group 3	Timolol maleate Propranolol No treatment	129 (32) 189 (46.9) 85 (21.1)
Gender	Female Male	280 (69.5) 123 (30.5)
One Location	Face Neck Extremity Scalp Body Visceral Genitalia	158 (39.2) 15 (3.7) 76 (18.9) 50 (12.4) 85 (21.1) 4 (1) 15 (3.7)
2./3. location (n = 48)	Neck Extremity Scalp Scalp + body Body Visceral Genitalia	2 (4.2) 9 (18.8) 12 (25) 1 (2.1) 19 (39.6) 1 (2.1) 4 (8.3)

Table2. *Distribution of information on follow-up and treatments*

	n	Median (range)
Follow-up time (months)	403	4 (0-28)
Treatment start age	318	6 (1-53)
		n (%)
During follow-up	stabilized shrunk grew up	114 (28.3) 243 (60.3) 46 (11.4)
TM initiation indication (n = 129)	Superficial hemangioma age < 6 months age = 6-12 months	43 (33.3) 64 (49.6) 22 (17.1)
P initiation indication (n = 189)	Facial hemangioma hemangioma in the neck Hemangioma larger than 2 cm Tends to grow bleeding ulceration Family request	92 48.7) 7 (3.7) 62 (32.8) 10 (5.3) 5 (2.6) 8 (4.2) 5 (2.6)
bleeding (n = 403)	none positive	397 (98.5) 6 (1.5)
ulceration (n = 403)	none positive	388 (96.3) 15 (3.7)
Abdomen USG (n = 403)	none No pathology Hemangioma positive	152 (37.7) 243 (60.3) 8 (2)
Cranial USG (n = 403)	none No pathology	216 (53.6) 187 (46.4)
Superficial USG (n = 403)	none No definitive diagnosis Hemangioma positive	297 (73.7) 27 (6.7) 79 (19.6)
ECO (n = 274)	none No pathology	143 (52.2) 131 (47.8)

TM: Timolol Maleate. **P**: Propranolol. **USG**: Ultrasonography. **ECO**: Echocardiography.

There was a significant difference between the groups regarding the mean age and mean age at diagnosis ($p < 0.05$). The mean age of children treated with P was significantly higher than that of those treated with TM (p: 0.030; $p < 0.05$). Additionally, the mean age at diagnosis of children treated with P was found to be significantly higher than that of those treated with TM (p: 0.036; $p < 0.05$). There were no significant differences among the other groups ($p > 0.05$) (Table 3).

No significant difference was observed between the groups concerning gender distribution ($p > 0.05$) (Table 3). The follow-up period for untreated children was significantly shorter compared to those treated with P (p: 0.001) and TM (p: 0.001) ($p < 0.05$). No significant difference existed between the P and TM groups ($p > 0.05$) (Table 3).

The age of treatment initiation in children treated with TM was statistically significantly lower than that in those treated with P (p: 0.001; $p < 0.05$). A statistically significant difference was observed among the groups concerning hemangioma locations (p: 0.001; $p < 0.05$). Facial IHs (54%) were significantly more prevalent in Group 2. The incidence of hemangiomas on the scalp (20.2%) in those treated with TM was significantly higher compared to those treated with P (6.9%). Furthermore, the proportion of hemangiomas on the trunk (12.2%) was significantly lower in individuals treated with P (Table 3).

Table 3. *Evaluations according to groups*

		TM Group 1	**PP Group 2**	**No Treatment Group 3**	**p**
Age (months) median		23	27	22	*
Age of diagnosis (months)		4	6	5	[1]0.039*
Follow-up time (months)		5	5	3	[1]0.001*
Age to start treatment (months)		5	6	-	[2]0.001*
Gender n (%)	Female Male	93 (%72.1) 36 (%27.9)	131 (%69.3) 58 (%30.7)	56 (%65.9) 29 (%34.1)	[3]0.626
Hemangioma location n (%)	Face Neck extremity Scalp Body Visceral Genitalia	38 (%29.5) 2 (%1.6) 24 (%18.6) 26 (%20.2) 34 (%26.3) 0 (%0) 5 (%3.9)	102 (%54) 10 (%5.3) 30 (%15.9) 13 (%6.9) 26 (%13.8) 2 (%1.1) 6 (%3.2)	18 (%21.2) 3 (%3.5) 22 (%25.9) 11 (%12.9) 25 (%29.5) 2 (%2.4) 4 (%4.7)	[3]0.001*
Response to treatment/no treatment n (%)	Stabil shrunk grew up	33 (%25.6) 70 (%54.3) 26 (%20.2)	37 (%19.6) 144 (%76.2) 8 (%4.2)	44 (%51.8) 29 (%34.1) 12 (%14.1)	[3]0.001*
Bleeding (%)	None pozitive	127 (%98.4) 2 (%1.6)	185 (%97.9) 4 (%2.1)	85 (%100) 0 (%0)	[4]0.493
Ulceration n (%)	None pozitive	123 (%95.3) 6 (%4.7)	180 (%95.2) 9 (%4.8)	85 (%100) 0 (%0)	[4]0.107
Abdomen USG n (%)	None no pathology Hemangioma	35 (%27.1) 93 (%72.1) 1 (%0.8)	86 (%45.5) 98 (%51.9) 5 (%2.6)	31 (%36.5) 52 (%61.2) 2 (%2.4)	[4]0.005*
Cranial USG n (%)	None No pathology	55 (%42.6) 74 (%57.4)	115 (%60.8) 74 (%39.2)	46 (%54.1) 39 (%45.9)	[3]0.006*
Superficial USG n (%)	None No definitive diagnosis Hemangioma	89 (%69) 12 (%9.3) 28 (%21.7)	142 (%75.1) 9 (%4.8) 38 (%20.1)	66 (%77.6) 6 (%7.1) 13 (%15.3)	[3]0.390
ECO n (%)	None no pathology		80 (%42.3) 109 (%57.7)	63 (%74.1) 22 (%25.9)	[3]0.001*

[1]Kruskal Wallis Test; [2]Mann Whitney U Test; [3]Ki-kare test; [4]Fisher Freeman Halton Exact Test
p < 0.05.* **TM: Timolol Maleate. **P**: Propranolol. **USG**: Ultrasonography. **ECO**: Echocardiography.

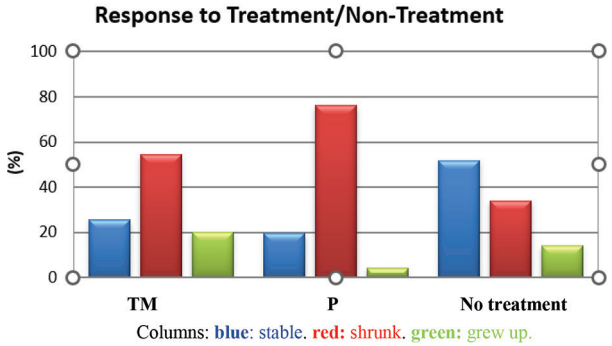

Figure 1. *Response toTreatment/Non-Treatment*

A significant difference emerged among the groups in terms of responses to treatment or lack thereof (p: 0.001; $p < 0.05$) (Table 3). The rate of hemangioma shrinkage in those treated with P (76.2%) was markedly higher than in those treated with TM (54.3%) and those who received no treatment (34.1%). Additionally, the shrinkage rate of hemangiomas in those treated with TM (54.3%) was significantly higher than in those who were untreated (34.1%) (Figure 1). No statistically significant differences were noted among the groups concerning bleeding and ulceration rates ($p > 0.05$) (Table 3). Notably, no side effects were reported.

DISCUSSION

Infantile hemangioma is one of the most common benign vascular endothelial tumors. Various approaches, including steroids, oral propranolol, topical timolol maleate, and laser therapy, are employed for treating infantile hemangioma (12, 13).

Since 2008, oral propranolol has gained widespread use for IH treatment (24). Numerous clinical trials have assessed the efficacy of oral propranolol for IH treatment. A meta-analysis has demonstrated that oral propranolol surpasses other therapies in improving the response rate of IH, thus being considered a first-line therapy for IH in children (25). In another study, P treatment achieved a therapeutic response with at least a 50% mean percentage reduction in size in 84.6% of patients (26). A study by Zhang et al. showed a response to oral propranolol treatment in 96.9% of 578 IH patients (27).

Although oral propranolol remains the primary IH therapy, topical timolol maleate offers a well-tolerated alternative. A study by Jha et al. confirmed the safety and effectiveness of topical timolol maleate for IH treatment (28). Another study involving 145 patients reported that only 8.3% showed no response to topical 0.5% timolol maleate treatment (29). Jha et al. also demonstrated that laser-assisted drug delivery of timolol maleate 0.5% is an effective and safe approach for treating deep IHs (30).

Despite these treatment options, infantile hemangiomas often regress spontaneously without complications (7, 9, 11). Thus, cases without complications, growth tendencies, or functional/cosmetic concerns can be managed without drug treatment (7).

According to our study results, oral propranolol emerged as the most effective IH treatment. No patient reported side effects. Topical timolol maleate therapy was primarily administered to infants under 6 months (p : 0.001) or for treating superficial IH, consistent with other studies. TM's treatment success rate was also high. However, P was predominantly administered to patients with growth tendencies and complications. If TM had been the initial treatment for these patients, TM's success rate might have been lower. Ongoing research investigates enhancing success rates by varying P and TM doses across different age groups. In our study, a dose of 2mg/kg/day proved effective for oral P. Larger studies are essential for assessing efficacy across various age groups.

The retrospective nature of our study limits it to information within patient records, constituting a study limitation.

CONCLUSION

Oral propranolol has demonstrated both effectiveness and safety in treating IH, whereas the efficacy of TM appears to be lower compared to P.

Author Contributions

Conceived and designed the analysis: OT; Collected the data: CNB, EA, AGK, EPU, HAS, DY, AOK, SE, ST, AA; Contributed data or analysis tools: OT; Performed the analysis: OT; Wrote the paper: OT.

Abbreviations

IH — Infantile hemangioma
P — Propranolol
TM — Timolol Maleate
USG — Ultrasonography.
ECO — Echocardiography

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Sažetak

ORALNI TOPIKALNI TIMOLOL MALEAT ILI ORALNI PROPRANOLOL U LEČENJU INFANTILNIH HEMANGIOMA: KLINIČKA ANALIZA 403 PACIJENTA

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Uvod: Infantilni hemangiomi (IH) predstavljaju najčešće benigne vaskularne tumore kod odojčadi. Propranolol (P), neselektivni beta-blokator, uspešno se primenjuje za tretiranje IH. Trenutno se istražuje efikasnost topikalnog β-antagoniste timolol maleata (TM) kod IH. **Cilj** ovog istraživanja je proceniti efekte intervencija u lečenju infantilnih hemangioma kod dece.

Materijal i Metode: Retrospektivno je analizirano ukupno 403 pacijenta sa IH dijagnozom u periodu od marta 2021. do marta 2022. godine. Pacijenti su podeljeni u tri grupe. Pacijenti u Grupi 1 su dobijali TM u dozi od jedne kapi topikalno, dva puta dnevno, 0,5%. Pacijenti u Grupi 2 su dobijali P u dozi od 1 mg/kg dva puta dnevno. Pacijenti u Grupi 3 nisu primili nikakav tretman, već je praćenje vršeno isključivo kontaktiranjem kontrolne grupe.

Rezultati: Srednja vrednost uzrasta pri postavljanju dijagnoze iznosila je 5 meseci (raspon 0-60), pri čemu je 57,1% slučajeva bilo muškog pola. Dok je TM tretman primenjen kod 32% dece, a P tretman kod 46,9% dece, 21,1% nije dobilo nikakav tretman. Najčešća lokacija hemangioma bilo je lice, što je činilo 39,2%. Hemangiomi su primećeni na više od jedne lokacije kod 48 (12%) dece. Srednja vrednost perioda praćenja pacijenata iznosila je 4 meseca (raspon 0-28). Hemangiomi su ostali nepromenjeni kod 28,3% svih slučajeva, smanjili su se kod 60,3%, a nastavili su rast kod 11,4%. Osnovni pokazatelj za započinjanje TM bio je površinski hemangiom i bebe mlađe od 6 meseci. Vodeći razlog za početak P tretmana bio je hemangiom na licu (p : 0,001). Stopa smanjenja IH kod osoba koje su tretirane P bila je značajno veća nego u drugim grupama (p : 0,001). Nisu primećene statistički značajne razlike između grupa u pogledu stope krvarenja i ulceracija (p > 0,05).

Zaključak: Efikasnost propranolola u tretiranju IH bila je veća u poređenju sa TM.

Ključne reči: timolol maleat, infantilni hemangiom, propranolol.

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