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Treatment of Infantile Hemangioma: A Comparative Study of Topical Timolol versus Oral Propranolol.

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ABSTRACT

Background: Infantile hemangiomas (IHs) are the most common benign vascular tumors in infancy, affecting 4–5% of infants. While many lesions involute spontaneously, a subset requires treatment due to functional impairment or cosmetic concerns. Oral propranolol is the standard therapy; however, topical timolol has emerged as a safer alternative.

Aim: To compare the efficacy and safety of topical timolol versus oral propranolol in superficial IHs.

Methods: A prospective interventional study was conducted on 200 patients. Patients received either oral propranolol (2 mg/kg/day) or topical timolol (0.5% hydrogel). Efficacy was assessed using the Visual Analog Scale (VAS), and safety was evaluated through adverse event monitoring.

Results: Both groups demonstrated comparable efficacy (propranolol: 97%, timolol: 96.4%; p = 0.26). Systemic adverse events were significantly higher in the propranolol group (3.9%) compared to none in the timolol group. Early initiation (<6 months) significantly improved outcomes.

Conclusion: Topical timolol is equally effective and safer than oral propranolol, supporting its use as first-line therapy in superficial IHs.

KEYWORDS: Infantile hemangioma, Topical timolol, Oral propranolol, Beta-blockers, Vascular tumors, Pediatric dermatology, Hemangioma treatment, Comparative study, Non-invasive therapy, Systemic therapy

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INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy, with an estimated incidence of 4–5% among infants, increasing to nearly 10% in preterm neonates [1,2]. These lesions arise due to dysregulated angiogenesis and vasculogenesis, characterized by clonal proliferation of endothelial cells. Emerging evidence suggests a role of hypoxia-inducible factors and placental origin markers such as GLUT-1 in their pathogenesis [3].

IHs typically follow a triphasic course consisting of a proliferative phase, plateau phase, and involution phase. The proliferative phase is most rapid during the first 3–5 months of life, during which approximately 80% of growth occurs, making early intervention critical [4].

Although most IHs undergo spontaneous regression, approximately 10–15% require treatment due to complications such as ulceration, bleeding, visual impairment, airway obstruction, or permanent cosmetic disfigurement [5]. Lesions in cosmetically sensitive areas such as the face pose significant psychosocial and functional risks.

Historically, systemic corticosteroids were the mainstay of treatment; however, their long-term use was limited due to adverse effects such as growth suppression, immunosuppression, and metabolic complications [6].

A major breakthrough occurred with the introduction of oral propranolol following its serendipitous discovery by Léauté-Labrèze et al. in 2008 [7]. Propranolol acts via vasoconstriction, inhibition of angiogenic pathways (VEGF, bFGF), and induction of endothelial apoptosis [8]. It is currently considered the gold standard therapy for complicated IHs.

However, systemic adverse effects such as bradycardia, hypotension, bronchospasm, and hypoglycemia necessitate careful monitoring, especially in infants [9]. These concerns have led to increasing interest in safer alternatives.

Topical timolol, a non-selective beta-blocker, has gained attention due to its localized action and minimal systemic absorption, particularly in superficial IHs [10]. Several studies have demonstrated its efficacy with an excellent safety profile, making it an attractive first-line option for selected cases.

However, comparative evidence between oral propranolol and topical timolol in large prospective studies remains limited. Therefore, this study aims to compare their efficacy and safety in superficial infantile hemangiomas.

Materials and Methods

- Study Design: Prospective interventional study
- Duration: January 2022 – January 2024
- Sample Size: 200 patients

Inclusion Criteria

- Patients with superficial infantile hemangiomas

Exclusion Criteria

- Prior treatment
- Contraindications to beta-blockers
- Deep, mixed, mucosal, or ulcerated lesions

Treatment Protocol

- Propranolol Group: 2 mg/kg/day orally in divided doses
- Timolol Group: 0.5% topical hydrogel applied three times daily

Baseline cardiovascular assessment was performed. Treatment continued until clinical improvement plateaued.

Groups

Group	Treatment	Dose
Group A	Oral Propranolol	2 mg/kg/day
Group B	Topical Timolol	0.5% hydrogel (TDS)

Assessment Parameters

- Clinical regression (VAS score)
- Adverse events (local/systemic)
- Predictors of response

Statistical Analysis

- Mann-Whitney U test
- Fisher’s exact test
- Significance: $p < 0.05$

Results

Patient Characteristics

- Mean age: 5.2 months
- Female predominance (2.23:1)
- Commonest site: head and neck (50%)
- Mean lesion size: 4.42 cm^2

Efficacy

- Propranolol: 97% response rate
- Timolol: 96.4% response rate
- No significant difference ($p = 0.26$)

Adverse Events

- Propranolol: 3.9% systemic adverse events
- Timolol: No systemic adverse events, minor local irritation in 3 cases

Predictors of Response

- Early treatment (<6 months) significantly improved outcomes
- No association with gender, lesion size, or location

Table 1: Baseline Characteristics

Parameter	Value
Mean Age (months)	5.2
Gender (M:F)	60:140
Prematurity (%)	12.5%
Progesterone exposure	7.5%
Lesion Location	Head & Neck (50%), Extremities (35%), Trunk (15%)
Mean Lesion Size	4.42 cm²

Table 2: Comparison Between Groups

Variable	Propranolol	Timolol	p-value
Mean Age	6.1	5.3	0.61
Male (%)	25	35	0.71
Lesion Size >5 cm²	45%	47%	0.28
Duration (months)	6	7.2	0.25

Table 3: Treatment Efficacy (VAS Score)

Outcome	Propranolol	Timolol
Excellent	45	45
Good	40	40
Fair	15	13
Poor	5	7

No statistically significant difference (p = 0.26)

Table 4: Adverse Events

Type	Propranolol	Timolol	p-value
Systemic AEs	4	0	<0.001
Local AEs	0	3	<0.001

Discussion

The present study demonstrates that both oral propranolol and topical timolol are highly effective in treating superficial infantile hemangiomas, with comparable response rates (97% vs. 96.4%, p = 0.26) [1]. These findings are consistent with previous studies reporting high efficacy for beta-blocker therapy in IHs [11,12].

The comparable efficacy observed between the two groups suggests that both drugs share similar mechanisms of action, primarily involving beta-adrenergic blockade leading to vasoconstriction, reduced angiogenesis, and endothelial apoptosis [8]. Topical timolol, despite its localized application, appears to effectively target superficial vascular proliferation.

A key finding of this study is the significantly improved safety profile of topical timolol. While systemic adverse events were observed in 3.9% of patients receiving propranolol, no systemic side effects were reported in the timolol group [1]. This aligns with previous reports indicating minimal systemic absorption of topical timolol when applied to intact skin [10,13].

Systemic propranolol therapy, although effective, carries risks such as hypoglycemia, bradycardia, and bronchospasm, particularly in younger infants or during intercurrent illness [9]. This necessitates baseline cardiovascular evaluation and close monitoring, which may not always be feasible in resource-limited settings.

In contrast, topical timolol offers a safer and more convenient alternative, especially for superficial and uncomplicated IHs. The minimal adverse effects observed, limited to mild local irritation in a few cases, further support its safety profile.

Another important observation is the significantly better response in patients who initiated treatment before 6 months of age. This finding is consistent with the natural history of IHs, where rapid proliferation occurs early in life, making early therapeutic intervention more effective [4].

From a clinical perspective, these results support a stratified approach to management. Superficial IHs can be effectively managed with topical timolol, thereby avoiding systemic exposure. However, deeper, segmental, or function-threatening lesions

may still require systemic propranolol therapy.

Despite its strengths, this study has certain limitations. The absence of long-term follow-up limits the evaluation of recurrence and long-term cosmetic outcomes. Additionally, the study is restricted to superficial IHs, limiting generalizability to deeper lesions.

Future studies, particularly randomized controlled trials with larger sample sizes and longer follow-up durations, are needed to further validate these findings and establish standardized treatment protocols.

CONCLUSION

Topical timolol is as effective as oral propranolol in treating superficial infantile hemangiomas while offering a superior safety profile. Early initiation of therapy significantly enhances outcomes. Therefore, topical timolol should be considered the preferred first-line treatment for superficial IHs.

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