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# EFFECTIVENESS OF ORAL PROPRANOLOL VERSUS TOPICAL TIMOLOL IN THE TREATMENT OF INFANTILE HEMANGIOMA – A CASE-CONTROL STUDY.

**[1]*Kranti Swagatika Guru, [2]Sanjib Kumar Meher, [3]Saujanya Behera**
*[1]Junior Consultant, Department of Pediatric Surgery, VSSIMSAR, Burla, Odisha, India.*
*[2]Assistant Professor, Department of Pediatric Surgery, VSSIMSAR, Burla, Odisha, India.*
*[3]Senior Resident, Department of Pediatrics Medicine, VSSIMSAR, Burla, Odisha, India.*



## Abstract

### Background

Infantile hemangiomas (IH) are the most common vascular tumors in infancy, with oral propranolol established as an effective treatment in 2008. However, due to systemic side effects, topical timolol has emerged as an alternative, necessitating a comparison of its efficacy and safety. This study aims to evaluate and contrast the effectiveness of oral propranolol versus topical timolol in treating infantile haemangiomas, focusing on their respective efficacy, safety profiles, and clinical outcomes.

### Methods

A prospective review was conducted at VSSIMSAR, Burla, over two years (January 2023 to January 2025), involving 104 children (3 months–4 years) with superficial infantile hemangiomas. Patients were randomized into two groups receiving either oral propranolol (1.5- 2 mg/kg daily) or topical timolol maleate (0.5% twice daily) for up to six months. Treatment response was assessed through lesion size reduction and classified using Achauer's four-point scale.

### Results

Both propranolol (95%) and timolol (93.4%) demonstrated high efficacy, with propranolol showing a faster response. At one month, 10 children in the propranolol group showed a significant reduction versus 5 in the timolol group. By six months, 45 and 42 children achieved marked improvement, respectively. Propranolol was associated with mild systemic side effects, while timolol was well-tolerated.

### Conclusion

Both propranolol and timolol effectively treated infantile hemangiomas, with propranolol acting faster but with mild systemic effects. Early intervention is crucial for optimal outcomes.

### Recommendation

Topical timolol is recommended as a safe and effective first-line treatment for superficial infantile hemangiomas, especially in cases where systemic side effects are a concern.

***Keywords:*** *Infantile hemangiomas, propranolol, timolol maleate, treatment efficacy, early intervention.*
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***Corresponding Author:*** *Kranti Swagatika Guru*
***Email:*** *krantiguru34@gmail.com*
*Junior Consultant, Department of Pediatric Surgery, VSSIMSAR, Burla, Odisha, India.*

## Introduction

Infantile haemangiomas (IH) represent the most prevalent benign vascular tumors found in infants, exhibiting a prevalence that varies between 1.2% and 12% among those under one year of age [1]. The majority of these lesions primarily arise in the head and neck area, representing around 60% of documented cases [1], although they may also appear on the trunk and limbs. Infantile hemangiomas follow a characteristic course, beginning shortly after birth and quickly advancing into a growth phase defined by rapid enlargement. At approximately one year of age, the advancement of tumors ceases, giving way to a process of regression. By the age of five, over fifty percent of these tumors completely resolve, with nearly seventy-five percent exhibiting full regression by the age of seven [2].

Historically, the approaches to managing IH have encompassed systemic corticosteroids, laser therapy, and surgical procedures, each presenting distinct levels of efficacy and possible adverse effects. In 2008, another study reported a notable advancement in the management of IH, identifying oral propranolol, a non-selective β-blocker, as an effective treatment that

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resulted in considerable regression of haemangiomas [3]. The effectiveness of propranolol in this scenario led to additional inquiries, and later research confirmed its ability to diminish lesion size, alter color, and mitigate related complications. Nonetheless, while systemic propranolol therapy demonstrates considerable efficacy, it is not without potential adverse effects. These may include bradycardia, hypotension, hypoglycemia, and bronchospasm, especially in individuals with pre-existing respiratory conditions like bronchial asthma.

To reduce systemic side effects, researchers investigated alternative methods, such as the use of topical β-blockers. In 2010, the pioneers in documenting the application of a non-selective β-blocker solution for the topical management of eyelid haemangiomas revealed encouraging therapeutic results [4]. Following this, yet another study [5] established that timolol maleate, a β-blocker frequently utilized in the treatment of glaucoma, demonstrated both safety and efficacy when administered topically for superficial haemangiomas. Due to its localized mechanism of action, topical timolol provides the benefit of focused treatment while minimizing the likelihood of systemic adverse effects [6,7].

As the treatment landscape for IH progresses, it is crucial to evaluate the efficacy and safety of systemic versus topical β-blockers to identify the most effective therapeutic strategy. This study seeks to evaluate and contrast the effectiveness of oral propranolol versus topical timolol in treating infantile haemangiomas, focussing on their respective efficacy, safety profiles, and clinical outcomes.

## Methods

### Study Design

This case control study was conducted to compare the efficacy and safety of oral propranolol and topical timolol in treating infantile hemangiomas. It employed a parallel-group design with a 1:1 allocation ratio and took placeat Veer Surendra Sai Institute of Medical Sciences and Research (VSSIMSAR), Burla, over a period of two years (January 2023 to January 2025).

### Sample Size

A total of 104 children, aged between 3 months and 4 years, both male and female, diagnosed with infantile hemangiomas (IH) were included. The hemangiomas were located on various anatomical sites, including the eyelids, lips, nose, ears, parotid, and cheek regions. The sample size of 104 children was determined based on prior literature indicating a high treatment response (~90%) to propranolol and timolol, with a power of 80% and a 5% margin of error to detect a 10% difference in efficacy between groups, allowing for a 10% dropout rate.

### Inclusion criteria

Patients under the age of four years with superficial haemangiomas and no prior treatment history were eligible for inclusion. Medical history, clinical examination, ultrasound, computed tomography, or magnetic resonance imaging determined the diagnosis. To ensure normal physiological parameters, chest radiographs, electrocardiograms, blood glucose levels, liver and renal function tests, and standard blood exams were performed.

### Exclusion criteria

Patients with extensive or combined vascular birthmarks, chronic airway inflammation, lung infection, advanced heart conduction abnormalities, slow heart rate, elevated body temperature, loose stools, and breathing-related infections were not included. A digitally generated allocation sequence assigned participants in equal proportions (1:1) to one of two therapeutic groups: oral beta-blocker medication or externally applied adrenergic antagonist gel.

### Randomization

### Sequence Generation

Random allocation was done using a computer-generated random number table.

### Type of Randomization and Restriction

Simple randomization without blocking was used.

### Allocation Concealment Mechanism

Sequentially numbered, opaque, sealed envelopes (SNOSE) were used to conceal the treatment allocation until after enrollment.

### Implementation

The randomization sequence was generated by an independent statistician. A pediatric dermatologist enrolled the participants, while allocation was performed by a separate study coordinator not involved in assessment or treatment.

### Blinding

The outcome assessors—a panel of three independent plastic surgeons—were blinded to treatment allocation. Clinical photographs were anonymized and coded before being evaluated using the Achauer four-point scale to ensure impartial assessment.

### Treatment Protocol

Children in the propranolol group received oral propranolol (10 mg tablets) at a dosage of 1.5 mg/kg once daily with food. Those in the topical timolol group were treated with 0.5% timolol maleate eye drops (25 mg/5 ml) and applied twice daily using a medical cotton

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swab. Care was taken to avoid application to the cornea or conjunctiva in cases of periocular hemangiomas.

Throughout the treatment period, infants were closely monitored for heart rate, blood pressure, and other vital signs. Parents were instructed to observe for potential side effects, including localized redness, loss of appetite, nausea, vomiting, wheezing, shortness of breath, or lethargy. In case of any adverse reactions, treatment was to be discontinued immediately, and parents were advised to closely monitor their child's condition. Regular follow-up assessments were conducted to evaluate lesion size and color changes. Treatment continued until complete regression of the lesion or for a maximum duration of six months if no improvement was observed.

## Efficacy and Safety Assessment

Treatment effectiveness was evaluated using clinical photographs taken at baseline, during treatment, and at the end of therapy. The dimensions of each lesion were recorded, and the percentage reduction in size was used as a measure of treatment response.

A panel of three independent surgeons, blinded to treatment groups, assessed the outcomes using a four-point scale proposed by Achauer et al.:

- **Class I (Poor):** Decrease in lesion size by <25%
- **Class II (Moderate):** Decrease in lesion size by 25%–50%
- **Class III (Good):** Decrease in lesion size by 50%–75%
- **Class IV (Excellent):** Decrease in lesion size by 75%–100%

Treatment was classified as effective if the response fell into Class III or IV, while Classes I and II were considered ineffective. Additionally, the occurrence of side effects and adverse events was documented to assess the safety of both treatment modalities. The primary outcome measure was the percentage reduction in lesion size, evaluated using Achauer's four-point scale. The secondary outcome measure was the incidence and nature of side effects or adverse events associated with each treatment modality.

## Statistical Methods

Data were analyzed using SPSS version 26.0. Categorical variables were compared using the Chi-square test. A p-value <0.05 was considered statistically significant. Subgroup analysis by age group and lesion site was also performed.

## Ethical Considerations

The study was approved by the Institutional Ethics Committee of Veer Surendra Sai Institute of Medical Sciences and Research (VSSIMSAR), Burla (Approval No: XXX).

## Results

Participants were recruited between January 1, 2023, and December 31, 2023, at the Veer Surendra Sai Institute of Medical Sciences and Research (VSSIMSAR), Burla. The follow-up period extended up to January 2025 to assess long-term outcomes and monitor adverse effects. Out of 122 children initially assessed for eligibility, 18 were excluded (10 did not meet inclusion criteria, and 8 declined to participate). A total of 104 children were randomized equally into two groups (52 each): oral propranolol and topical timolol. All randomized participants received the intended treatment. Two participants (one from each group) were lost to follow-up by the sixth month due to migration, and their data were excluded from the final efficacy analysis but included in the safety analysis.

Table 1 presents the demographic and clinical characteristics of the two groups. No significant differences were observed between groups at baseline.

**Table 1. Baseline Demographic and Clinical Characteristics**

| Characteristic | Propranolol (n=52) | Timolol Maleate (n=52) |
|---|---|---|
| Mean age at treatment (months) | 10.2 ± 2.5 | 10.5 ± 2.3 |
| Gender (Male/Female) | 28 / 24 | 27 / 25 |
| Lesion location (%) | | |
| – Eyelid | 9 (17.3%) | 10 (19.2%) |
| – Lip | 8 (15.4%) | 7 (13.5%) |
| – Nose | 7 (13.5%) | 6 (11.5%) |
| – Parotid | 14 (26.9%) | 13 (25.0%) |
| – Cheek | 14 (26.9%) | 16 (30.8%) |
| Type of hemangioma | | |
| – Superficial | 39 (75%) | 40 (76.9%) |
| – Complex | 13 (25%) | 12 (23.1%) |
| Gestational age <37 weeks | 5 (9.6%) | 4 (7.7%) |
| Maternal progesterone use | 3 (5.8%) | 4 (7.7%) |

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Both oral propranolol and topical timolol maleate demonstrated high effectiveness in treating infantile hemangiomas, with success rates of 95% and 93.4%, respectively. However, propranolol exhibited a faster response, as evidenced by a greater number of effective treatments at earlier time points. At one month, 10 children treated with propranolol showed a significant reduction in hemangioma size compared to 5 children in the timolol group. By three months, the response rate increased to 25 in the propranolol group and 22 in the timolol group. After six months, 45 children in the propranolol group and 42 in the timolol group achieved a marked reduction in lesion size, confirming the overall effectiveness of both treatments.

The mean duration of treatment was similar for both groups, with propranolol requiring an average of 5.2 months, while timolol maleate showed comparable results with a treatment duration of 5.0 months. Notably, propranolol treatment was associated with side effects, including mild systemic symptoms, whereas topical timolol maleate was well-tolerated, with no reported adverse effects.

Further analysis revealed no significant differences in clinical outcomes based on gender, lesion location and size, treatment duration, gestational age, or maternal progesterone use during pregnancy. However, the type of hemangioma influenced treatment efficacy, with superficial hemangiomas responding more favorably than complex hemangiomas. Additionally, the timing of treatment initiation played a crucial role, highlighting the importance of early intervention for optimal therapeutic outcomes.

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**Table 1: Treatment Effectiveness in Infantile Hemangiomas**

| Variable | Propranolol (n=52) | Timolol Maleate (n=52) |
|---|---|---|
| **Effective treatment (Classes III and IV)** | | |
| At 1 month | 10 | 5 |
| At 3 months | 25 | 22 |
| At 6 months | 45 | 42 |
| **Mean (SD) duration of treatment (months)** | 5.2 (±0.8) | 5.0 (±0.7) |

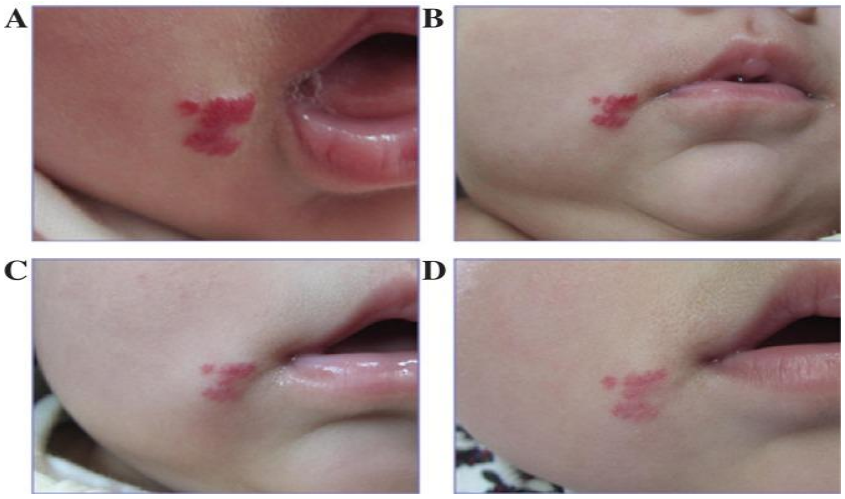


**Figure 1: Topical timolol for the treatment of infantile hemangiomas (A) before timolol treatment, and after (B) 1 month, (C) 3 months, (D) 6 months.**

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## Discussion

Infantile hemangiomas, the most common benign tumors in infancy, affect 4%–10% of children, more often females, and typically appear before one year of age, undergoing rapid growth followed by slow involution [8]. Nevertheless, despite regression, telangiectasia, scarring, persistent adipose tissue, and epithelial atrophy occur in approximately 40–50% of cases [9, 10]. When haemangiomas involve essential structures such as the eyelids or larynx, they may compromise vision or present serious health risks, thereby requiring prompt intervention instead of mere observation [11]. Strategies for treatment ought to be customized according to the growth phase of the lesion to enhance outcomes.

Haemangiomas are categorized according to their depth into three distinct types: superficial, which is limited to the papillary dermis; deep, which penetrates the reticular dermis and subcutaneous tissue; and mixed types, which encompass both superficial and deep elements. Considering the diverse manifestations, it is crucial to adopt a tailored therapeutic strategy that takes into account factors such as the location, size, and depth of the lesion to achieve the best possible outcomes. At present, the emphasis is on medical management rather than surgical interventions, with a variety of pharmacological options accessible based on the specific indication. Traditionally, systemic corticosteroids have been regarded as the primary treatment option; nevertheless, their extended application is linked to various negative outcomes, such as immune suppression, cushingoid characteristics, and growth retardation [12,13].

Propranolol, functioning as a non-selective β-adrenergic antagonist, provides targeted therapeutic benefits, demonstrating superior efficacy and tolerance in comparison to corticosteroids, all while reducing the likelihood of adverse reactions [14–16]. Timolol maleate, another β-blocker, serves as a powerful non-selective antagonist of both β1- and β2-adrenergic receptors and is primarily indicated for the management of hypertension, angina, tachycardia, and glaucoma. Documented adverse reactions encompass hypotension, hypoglycemia, bronchospasm, and localized pruritus. Timolol, approved for the treatment of glaucoma in 1978, has found extensive application in pediatric ophthalmology, supported by a well-documented safety profile [17].

The minimal local irritation and low systemic absorption associated with timolol maleate render it an appropriate topical option for the treatment of superficial haemangiomas. In 2010, Guo and Ni [4] initially reported the successful application of this treatment in a 4-month-old infant presenting with a capillary haemangioma of the eyelid, a discovery that has since been corroborated by numerous subsequent studies. One study [18] documented notable advancements in six instances of haemangiomas addressed with topical timolol, whereas Wang et al. [19] illustrated its effectiveness in a group of 25 children receiving a 0.5% solution. Current research indicates that the pharmacological potency of timolol is roughly eightfold greater than that of propranolol [5]. This allows for dose reduction in oral propranolol when combined with topical timolol, thereby enhancing safety and minimizing adverse effects.

Clinical studies have shown that oral propranolol alone effectively reduces hemangioma size over 6–10 months [20,21]. This study evaluated the effectiveness of propranolol and timolol maleate, each used independently, in managing superficial hemangiomas. While both treatments were effective, propranolol led to a faster response, whereas timolol was associated with fewer side effects. These findings align with previous research, underscoring the importance of tailoring treatment strategies based on lesion characteristics and patient safety.

## Conclusion

This study demonstrated that both oral propranolol and topical timolol maleate are highly effective in treating infantile hemangiomas, with success rates of 95% and 93.4%, respectively. While propranolol resulted in a faster response, it was associated with mild systemic side effects, whereas timolol was well-tolerated with no reported adverse effects. Early intervention was found to enhance treatment outcomes, particularly for superficial hemangiomas. Given its safety profile, topical timolol may serve as a preferred first-line treatment, while propranolol remains an effective alternative for cases requiring a more rapid therapeutic response.

## Generalizability

The study's findings are most applicable to infants with superficial hemangiomas and may not extend to deeper or mixed types. As it was conducted in a single-center setting with a homogenous population, extrapolation to diverse demographic or geographic populations should be done with caution. Broader multicenter studies would enhance external validity.

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## Limitations
The study was limited by a modest sample size, a lack of blinding, and a short follow-up period. These constraints could affect the accuracy of treatment comparisons and the assessment of long-term outcomes or cosmetic sequelae. Additionally, combined therapy was not evaluated, though it may offer synergistic benefits.

## Recommendation
Timolol maleate is recommended for small, superficial lesions due to its safety and tolerability, while propranolol remains the first-line agent for extensive or deep hemangiomas. Treatment should be individualized based on lesion characteristics and patient factors. Future studies should explore combination regimens and long-term results.

## Acknowledgment
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## Conflict of Interest
The authors declare no conflict of interest.

## Author Contributions
All authors contributed equally to this study.

## Data Availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

## Trial Registration
NA

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