https://doi.org/10.29309/TPMJ/2025.32.07.9830

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 07

ORIGINAL ARTICLE

Efficacy and safety of combined oral propranolol, oral prednisolone, and topical timolol versus combination of oral propranolol plus topical timolol in treating infantile hemangioma.

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Article Citation: Rafique A, Shahid M, Sheikh S, Asghar F, Ali N, Ahmad S, Ahsan M. Efficacy and safety of combined oral propranolol, oral prednisolone, and topical timolol versus combination of oral propranolol plus topical timolol in treating infantile hemangioma. Professional Med J 2025; 32(07):909-914. https://doi.org/10.29309/TPMJ/2025.32.07.9830

ABSTRACT… Objective: To determine the efficacy and safety of combined oral propranolol, oral prednisolone, and topical timolol in treating infantile hemangioma. **Study Design:** Randomized Clinical Trial. **Setting:** Department of Dermatology, Allied II (DHQ) Hospital Faisalabad Medical University, Faisalabad. **Period:** November 23 to September 24. **Methods:** A total of 68 infants (up to 1 year of age) to children up to 3 years of age with clinically diagnosed infantile hemangiomas (IHs) were enrolled through non-probability consecutive sampling. Infants with comorbidities such as asthma, cardiac disease, or prior treatment were excluded. Participants were randomized into two groups: Group D (dual therapy) received dual therapy (oral propranolol and topical timolol only) while Group T (Triple) received triple therapy (oral propranolol, oral prednisolone, and topical timolol). Patients were followed biweekly for the first month and monthly thereafter for three months. Treatment efficacy was assessed based on lesion regression, while secondary outcomes included side effects and parental satisfaction. **Results:** Improvement (25–100% reduction) was observed in 88% of patients in Group D and 97% of patients in Group T, But not statistically significant. However, the incidence of mild-to-moderate side effects was notably higher in Group D (32%) compared to Group T (6%), which was statistically significant. **Conclusion:** Both the combinations of oral propranolol, oral prednisolone, and topical timolol and the combination of oral propranolol and topical timolol demonstrated high efficacy, but triple therapy had better results with less complications.

Key words: Combination Therapy, Infantile Hemangioma, Prednisolone, Propranolol, Timolol.

INTRODUCTION

Affecting 5–10% of newborns, infantile hemangioma (IH) is the most frequent benign vascular tumor in infants. It usually presents as a red or raised lesion on the skin or subcutaneous tissues, varying widely in appearance. IHs emerge within weeks after birth, grow quickly, and undergo spontaneous regression over time.[1-3] The pathogenesis of infantile hemangiomas is not fully understood, but various explanations exist. The leading theory posits that hypoxia triggers the upregulation of GLUT-1 and VEGF, activating endothelial progenitor cells that express CD133 and CD31. An alternative hypothesis proposes that placental trophoblasts contribute stem cells responsible for hemangioma formation. Additionally, some researchers suggest a combination of vasculogenesis and angiogenesis, with angiogenic signals promoting new capillary development through interactions with endothelial cells and pericytes.[4-5]

Head and neck regions are commonly affected by IHs primarily, however, it can appear on the body anywhere. Typically, they are spotted in early days of life and become a significant challenge due to their potential to cause significant complications, including auditory and visual impairment, bleeding, ulceration, and airway obstruction.[6]

Over the years, various therapeutic approaches have been employed to manage IHs, including pharmacologic treatments, surgical excision, and laser therapy.[7]

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Article received on: 01/04/2025
Accepted for publication: 02/06/2025

Historically, systemic corticosteroids were the mainstay treatment due to their anti-inflammatory properties and ability to inhibit angiogenesis. However, the introduction of propranolol, a non-selective beta-blocker, marked a breakthrough in the treatment of infantile hemangioma by targeting multiple pathways—causing blood vessel constriction, reducing new blood vessel formation, and promoting programmed cell death in endothelial cells.[8]

Extensive evidence supports the use of propranolol in infantile hemangiomas, showing substantial improvement in both the size and pigmentation of the lesions.[9] According to recent developments, the efficacy of a beta-blocker i.e. topical timolol, is highlighted for the management of superficial IHs, showing a higher reduction rate in in lesion size and color with reduced systemic adverse effects.[10] Various clinical studies capitalized that the synergistic use of topical timolol and oral propranolol offers significant improved outcomes in the management of IHs compared to monotherapy with either agent.[7] This study recommended that a combination of oral prednisolone and oral propranolol, and topical timolol is effective and safe than monotherapy. For outpatients, this regimen is suitable, requiring no adjunctive laser therapy, hospital admission and cardiac evaluation. Remarkably, 77.47% of the cases achieved marked to complete resolution within 3 months.[11]

For situations demanding prompt clinical improvement, oral corticosteroids remain a key element in combination regimens for treating infantile hemangiomas.[12-13] Considering the complexities and potential adverse effects associated with individual treatment options, the combined use of oral propranolol, oral prednisolone, and topical timolol offers a promising therapeutic strategy for infantile hemangiomas. This multimodal approach capitalizes on the synergistic effects of each agent, facilitating a rapid and sustained response while reducing the risk of side effects. Existing literature supports that such combination regimens enhance efficacy, improve tolerability, and shorten treatment duration compared to single-drug therapies.

The management of infantile hemangiomas (IHs) continues to pose a clinical challenge due to their potential for serious complications and the need for reliable, effective treatments. This study aims to address the existing gap in knowledge regarding optimal therapeutic strategies, particularly for cases demanding a rapid and sustained response. By evaluating the combined use of oral propranolol, oral prednisolone, and topical timolol, the study seeks to establish a comprehensive treatment approach. The findings may contribute to improved clinical outcomes, shortened treatment durations, and reduced adverse effects, ultimately enhancing the quality of life for affected infants and their families.

METHODS

This randomized clinical trial was conducted at the Dermatology Department, Allied 11 (DHQ) Hospital, Faisalabad Medical University, over a period of ten months (November'23 to September'24) after approval from the IRB (Letter No: 48.ERC/FMU/2023/540, Dated: 26-11-2023). The sample size was calculated using the WHO sample size calculator, based on an expected percentage of 77.47% patients achieving marked to complete clearance, with an absolute precision of 10% and a 95% confidence level. The resulting sample size was 68. Infants (up to 1 year of age) to children up to 3 years of age diagnosed with infantile hemangiomas (IHs), including both superficial and deep types, with either single or multiple lesions, were enrolled through non-probability consecutive sampling after obtaining informed parental consent. Infants with asthma, cardiac disease, arrhythmias, diabetes, hypo/hypertension, known hypersensitivity to study drugs, prior treatment for IHs, or vascular malformations were excluded.

Eligible patients were randomly divided into two groups: Group T (triple therapy) and Control Group D (Dual therapy). Group T received a triple therapy consisting of oral propranolol (1–2 mg/kg/day in two divided doses, starting at 1 mg/kg/day for the first two weeks, then increased to 2 mg/kg/day), oral prednisolone (0.5 mg/kg/

day for one month, followed by tapering over three weeks), and topical timolol 0.5% drops applied twice daily. Group D received only oral propranolol and topical timolol in the same doses and frequency.

All patients underwent a baseline evaluation including clinical history, physical examination, blood glucose testing, complete blood count, renal and liver function tests. Electrocardiography and echocardiography were performed in selected cases to assess cardiac status. The first dose of propranolol was administered under monitored conditions during a short hospital admission. Heart rate and blood pressure were recorded before administration and at 30-minute intervals for four hours post-dose.

Patients were followed biweekly during the first month and then monthly for a total of three months. The primary outcome—efficacy of treatment—was assessed by observing changes in the size and color of the hemangioma, categorized into two levels of regression: poor (0–25%), moderate to complete clearance (25–100%). Secondary outcomes included safety (measured by incidence of adverse effects).

Data were analyzed using SPSS version 26. Descriptive statistics were used for baseline characteristics. Chi-square tests were applied to compare categorical variables such as regression scores and satisfaction levels between groups. Paired t-tests were employed for comparing continuous variables within groups. Frequency distributions were used to evaluate safety profiles. A p-value <0.05 was considered statistically significant.

RESULTS

The age distribution showed that a majority, 57.4% (n = 39), were older than 12 months, while 42.6% (n = 29) were 12 months or younger. Gender distribution revealed a slight female predominance, with 55.9% (n = 38) being female and 44.1% (n = 30) male. Regarding family history of infantile hemangioma (IH), 19.1% (n = 13) of patients had a positive family history, while 80.9% (n = 55) did not. In terms of lesion type, 66.2% (n = 45) of the hemangiomas were classified as superficial and 33.8% (n = 23) as deep. The most common anatomical location of IHs was the head and neck region (55.9%, n = 38), followed by the trunk (25.0%), limbs (14.7%), and multiple sites (4.4%). The predominant color observed was bright red (55.9%, n = 38), followed by purple (29.4%, n = 20) and dusky lesions (14.7%, n = 10). The mean age of the infants was 7.10 ± 3.52 months, and the mean number of lesions per patient was 1.68 ± 0.72.

When comparing the treatment outcomes between Group T (oral propranolol, oral prednisolone, and topical timolol) and Group D (oral propranolol and topical timolol only). Efficacy in terms of regression score, 25–100% resolution was seen to be better in triple therapy, with 33/34 patients (97%) from group T showed marked to complete lesion clearance, compared to 30/34 (88%) in the group D. Poor response (0–25%) was observed in 4 patients (11.8%) in Group D and one patient (2.9%) in Group T. The difference in regression scores between the two groups was not statistically significant ($p = 0.35$). The odds ratio was 0.227, indicating lower odds of success in Group D compared to Group T. However, Fisher's exact test revealed that the difference was not statistically significant ($p > 0.05$).

Mild-to-moderate side effects were observed in 32% of patients in Group D versus 6% in Group T. The odds ratio for absence of side effects was 0.13, favoring Group T. Fisher's exact test showed this difference was statistically significant ($p < 0.05$).

DISCUSSION

In this study evaluating the treatment of infantile hemangioma, both the combination of oral propranolol, oral prednisolone, and topical timolol (Group T) and the combination of oral propranolol and topical timolol (Group D) demonstrated high efficacy. Significant improvement (25–100% reduction) was observed in 88% of patients in Group D and 97% of patients in Group T, with no statistically significant difference between the groups. However, the incidence of mild-to-

moderate side effects was notably higher in Group D (32%) compared to Group T (6%), and this difference was statistically significant.

Variable	Category	Count (%)
Age Group	≤12 months	29 (42.6%)
	>12 months	39 (57.4%)
Gender	Male	30 (44.1%)
	Female	38 (55.9%)
Family History	Yes	13 (19.1%)
	No	55 (80.9%)
Type of IH	Superficial	45 (66.2%)
	Deep	23 (33.8%)
Location of IH	Head/Neck	38 (55.9%)
	Trunk	17 (25.0%)
	Limbs	10 (14.7%)
	Multiple	3 (4.4%)
Color of IH	Bright Red	38 (55.9%)
	Purple	20 (29.4%)
	Dusky	10 (14.7%)
Mean Age in Months	-	7.10 ± 3.52
Mean No. of Lesions	-	1.68 ± 0.72

Table-I. Demographic and clinical characteristic (N = 68)

Outcome		Group D (Count %)	Group T (Count %)	P- Value
Efficacy on terms of Re-gression score	25–100%	30 (88%)	33 (97%)	0.35
	0–25%	4 (12%)	1 (3%)	
Side Effects	None	23 (67.6%)	32 (94.1%)	0.02
	Mild-Moderate	11 (32%)	2 (6%)	

Table-II. Efficacy and safety of combined oral propranolol, oral prednisolone, and topical timolol versus combination of oral propranolol plus topical timolol in treating infantile hemangioma (N=68)

Our findings are partially consistent with a previous study[11], which reported 77.47% clearance with the triple regimen within three months, along with the claim of good safety and outpatient applicability. A major comparative reference is the study by Sharquie and Jabbar (2023)[15], who treated 182 infants using the same triple regimen and reported up to 75–100% clearance within 3–6 months, without any adverse effects noted during the treatment course. Compared to the current study, their results suggest higher efficacy and better tolerability. The discrepancy in side effect reporting may be attributed to differences in setting (home-based vs. hospital-monitored), side effect documentation, or observer bias.

The meta-analysis by Qiao et al. (2020)[16] further supports combination therapy, finding that oral propranolol plus topical timolol was significantly more effective than either agent alone, with a 14% increase in response rate (RR = 1.14, p = 0.03) over propranolol alone and 36% over timolol alone (RR = 1.36, p = 0.01). However, it found no significant increase in adverse effects when compared to monotherapy. In contrast, the present study shows a notable increase in mild-to-moderate side effects when prednisolone is added, suggesting that the third agent may be contributing to reduced tolerability.

The systematic review by Huang et al. (2024)[17] echoes similar efficacy findings, highlighting that both propranolol and timolol are effective, and their combination improves clinical outcomes without significantly elevating risks. These conclusions support the dual therapy approach as an effective and relatively safe option. Han et al. (2024)[18] compared oral propranolol with topical timolol for superficial IHs and noted that propranolol offers faster and deeper resolution but has more systemic side effects. Topical timolol was safer but slower in effect. These findings align with the rationale for combination therapy in the current study and the attempt to balance rapid response with safety. Similarly, the study by Rehan et al. (2024)[19] from Peshawar found no significant difference in efficacy or safety between oral propranolol and topical timolol monotherapies (excellent response in 42.5% vs. 45%, p = .624) . These results justify the use of both agents together but also highlight that monotherapies can be effective in selected cases.

Lastly, a study by M Alzaid and others[20] reveal that the use of timolol in several dermatological

conditions is well-tolerated and is becoming increasingly popular in dermatology including IH, pyogenic granulomas, Kaposi sarcoma, chronic wound healing, postsurgical wounds, acne vulgaris, rosacea, eczema and red scrotum syndrome.

One of the key strengths of this study is its randomized design, which enhances the internal validity and minimizes selection bias in the comparison between triple and dual therapy for infantile hemangiomas. By directly evaluating both efficacy and safety outcomes, including regression scores, and adverse effects, the study provides comprehensive clinical insight into the relative performance of the two treatment regimens. Another strength of this study is the practical, outpatient-based approach to therapy, which supports the applicability of the findings in real-world and resource-limited settings.

LIMITATIONS

However, the study has certain limitations. The relatively short follow-up duration of three months limits the ability to assess long-term outcomes such as recurrence or delayed adverse effects. Additionally, reliance on subjective assessments for lesion regression and parent-reported satisfaction introduces potential for observer and reporting bias. Lastly, although adequately powered, the modest sample size may restrict the detection of less common adverse events and limit subgroup analyses.

CONCLUSION

Both the combinations of oral propranolol, oral prednisolone, and topical timolol and the combination of oral propranolol and topical timolol demonstrated high efficacy, but triple therapy had better results with less complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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1	**Aqsa Rafique:** Data collection, analysis, paper writing.
2	**Muhammad Shahid:** Discussion writing, review manuscript.
3	**Saifullah Sheikh:** Data collection, paper writing.
4	**Faizaan Asghar:** Data collection, entry.
5	**Nadia Ali:** Literature review, data entry.
6	**Shakeel Ahmad:** Review of manuscript.
7	**Muhammad Ahsan:** Data analysis, manuscript writing.