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MANAGEMENT AND THERAPEUTIC OUTCOMES OF INFANTILE HEMANGIOMAS IN THE PERIOCULAR REGION: A REVIEW

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ABSTRACT

Background: Infantile hemangiomas (IHs) are benign vascular tumors of early childhood characterized by rapid postnatal proliferation followed by spontaneous involution. When localized to the periocular region, these lesions present substantial functional risks, including visual axis obstruction, astigmatism, and amblyopia.
Aim: The objective of this review is to evaluate the diagnostic dynamics, ultrasound characteristics, and therapeutic efficacy of topical and systemic beta-blocker therapies in managing periocular infantile hemangiomas.
Material and Methods: A comprehensive synthesis of clinical guidelines, consensus statements, and literature regarding periocular infantile hemangiomas, diagnostic imaging, and beta-blocker management protocols was conducted.
Results: Periocular hemangiomas frequently exhibit aggressive early volumetric growth, transitioning from ambiguous superficial lesions to large mixed tumors with robust vascular signals. While topical beta-blockers (such as timolol) are effective for thin superficial components, rapidly progressing mixed and deep lesions necessitate systemic propranolol therapy. Standard dosing regimens titrated to approximately 2 mg/kg/day consistently achieve profound tumor involution, prevent permanent visual impairment, and demonstrate favorable long-term safety profiles.
Conclusion: Early multidisciplinary evaluation, serial ultrasound monitoring, and prompt initiation of beta-blocker therapy are crucial for optimizing functional and aesthetic outcomes in children with periocular infantile hemangiomas.

KEYWORDS

Infantile Hemangioma, Periocular Region, Propranolol, Timolol, Ultrasound

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Introduction

The International Society for the Study of Vascular Anomalies (ISSVA) and leading pediatric dermatology consensus statements emphasize that biological classification, functional visual monitoring, and vascular risk assessments should be seamlessly integrated into pediatric clinical evaluation standards (Goldenberg et al., 2025; Krowchuk et al., 2019). Infantile hemangiomas (IHs) represent the most prevalent benign vascular tumors of early childhood, affecting up to 10% of infants (Kwon et al., 2013; Macca et al., 2022). These tumors display a unique endothelial proliferative profile characterized by a rapid postnatal expansion phase during the first months of life, followed by a plateau phase and eventual spontaneous involution spanning several years (Gong et al., 2025; Storch & Hoeger, 2010). Although the majority of small, superficial cutaneous hemangiomas follow a self-limiting course requiring only clinical surveillance, lesions localized to the periocular region constitute a high-risk category associated with severe structural and visual complications (Samuelov et al., 2018; Zhao et al., 2019).

The critical clinical significance of periocular infantile hemangiomas is dictated by their intimate anatomical proximity to the developing visual axis and orbital structures (Al-Haddad et al., 2019; Tran et al., 2016). Rapid tumor growth within the eyelid, medial canthus, or retrobulbar space frequently induces mechanical ptosis, visual axis occlusion, and localized compression of the globe (Chen et al., 2020; Herlihy et al., 2016). This biomechanical pressure distorts corneal curvature, inducing high astigmatism and anisometropia that can trigger irreversible deprivation or refractive amblyopia if left unmanaged during critical neuro-developmental windows (Herlihy et al., 2016; Samuelov et al., 2018). Furthermore, the presence of an occult deep subcutaneous component often obscures the true volumetric extent of the mass upon superficial physical examination, leading to early diagnostic uncertainty (Ginguerra et al., 2018; Kutz et al., 2015).

A primary diagnostic challenge in managing rapidly progressive periocular lesions is differentiating deep vascular tumors from post-traumatic hematomas, venous malformations, or soft-tissue neoplasms during the early proliferative phase (Goldenberg et al., 2025; Kutz et al., 2015). Relying solely on initial clinical inspection can be deceptive, as deep subcutaneous hemangiomas may lack classic cutaneous erythema or display minimal Doppler vascular signals on preliminary screening (Ginguerra et al., 2018). High-resolution

soft-tissue ultrasonography paired with color Doppler imaging plays an indispensable role in capturing dynamic shifts in lesional volume, margins, and intrinsic blood flow velocity, thereby guiding timely clinical decision-making (Kutz et al., 2015; Ye et al., 2012).

The management paradigm for problematic infantile hemangiomas underwent a historical shift following the discovery of the therapeutic potential of non-selective beta-blockers (Léauté-Labrèze et al., 2015; Storch & Hoeger, 2010). Systemic oral propranolol replaced surgical resections and high-dose corticosteroid regimens as the first-line gold standard for hemangiomas threatening vital functions or visual development (Krowchuk et al., 2019; Smithson et al., 2017). Propranolol acts through localized vasoconstriction, down-regulation of pro-angiogenic factors (such as VEGF and bFGF), and induction of endothelial cell apoptosis (Storch & Hoeger, 2010). Standard oral dosing regimens titrated to approximately 2–3 mg/kg/day consistently achieve rapid tumor regression, clearance of the deep subcutaneous mass, and prevention of amblyopia (Adams & Ryan, 2022; Malvindi et al., 2025).

Concurrently, topical beta-blocker modalities—such as 0.5% timolol maleate drops or gel—have emerged as a targeted alternative for small, thin, superficial cutaneous hemangiomas, offering localized efficacy while minimizing systemic pharmacological exposure (Han et al., 2024; Ye et al., 2012). However, for mixed or deep periocular hemangiomas featuring significant subcutaneous enlargement, topical therapy alone is insufficient to penetrate deeper orbital tissues, necessitating systemic intervention or combination management strategies (Han et al., 2024; Qiao et al., 2020). Despite the outstanding efficacy of oral propranolol, clinicians must balance therapeutic benefits against potential adverse effects (including hypoglycemia, bradycardia, and hypotension) and manage the risk of post-treatment rebound growth following drug cessation (Baruch et al., 2024; Ghahvehchian et al., 2024; Shah et al., 2016).

Beyond the operational differences between single-agent regimens, recent clinical investigations have evaluated combination therapies to enhance resolution rates in complex periocular presentations (Qiao et al., 2020). Concurrent administration of low-dose oral propranolol with adjunct topical timolol maleate has been shown to accelerate superficial color regression while maintaining targeted systemic suppression of the deep subcutaneous proliferative component (Han et al., 2024; Qiao et al., 2020). Furthermore, alternative systemic beta-blockers, such as oral atenolol, are increasingly studied due to their hydrophilic properties and selective beta-1-adrenergic antagonism, which may offer a reduced incidence of central nervous system side effects (such as sleep disturbance and lethargy) compared to lipophilic propranolol (Baruch et al., 2024; Ji et al., 2021). Nevertheless, oral propranolol remains the benchmark against which novel therapeutic protocols and alternative pharmacotherapies are rigorously compared (Hu et al., 2026; Léauté-Labrèze et al., 2015).

High-resolution serial ultrasonography with high-frequency transducers serves as an indispensable tool not only for baseline diagnostic clarification but also for objective quantitative monitoring throughout the therapeutic lifecycle (Kutz et al., 2015; Zhao et al., 2011). Quantitative evaluation of maximum linear dimensions, tissue echogenicity, and Doppler peak systolic velocity allows clinicians to accurately distinguish between active vascular proliferation, drug-induced stabilization, and true structural involution (Ginguerra et al., 2018; Kutz et al., 2015). This objective imaging approach is especially crucial when deciding the optimal timing for drug tapering, as clinical reliance on cutaneous appearance alone can mask persistent, deep-seated subcutaneous activity (Ginguerra et al., 2018; Shah et al., 2016). Implementing systematic ultrasound monitoring protocols reduces the risk of premature treatment cessation and subsequent rebound growth (Gong et al., 2025; Shah et al., 2016).

Long-term interdisciplinary follow-up represents the final essential pillar in the overall management of periocular infantile hemangiomas (Ghahvehchian et al., 2024; Mazhar et al., 2020). Although complete resolution of the vascular lesion can be achieved via systemic beta-blocker therapy, secondary structural residual changes—such as minimal fibrofatty tissue deposition, subtle cutaneous telangiectasias, or mild persistent astigmatic refractive errors—may persist into early childhood (Al-Haddad et al., 2019; Herlihy et al., 2016; Zhao et al., 2019). Sustained collaboration between pediatric dermatologists, pediatric ophthalmologists, and pediatric surgeons ensures that post-involution visual acuity, binocular alignment, and aesthetic outcomes are systematically tracked, thereby optimizing the child's long-term visual development and overall quality of life (Krowchuk et al., 2019; Smithson et al., 2017).

Understanding the long-term clinical trajectories of periocular infantile hemangiomas requires a comprehensive synthesis of early diagnostic imaging, multidisciplinary ophthalmic risk stratification, standardized beta-blocker dosing protocols, and post-treatment monitoring frameworks (Hu et al., 2026; Mazhar et al., 2020). Resolving diagnostic ambiguities and optimizing pharmacological pathways are essential

for protecting visual function, maintaining ocular alignment, and achieving superior aesthetic outcomes in pediatric patients (Ji et al., 2021; Zhao et al., 2011).

This narrative review aims to synthesize current clinical and empirical data regarding the physiological behavior, ultrasound characteristics, and therapeutic outcomes of periocular infantile hemangiomas. Specifically, it addresses the dynamic volumetric evolution of mixed-type lesions, the comparative efficacy of topical timolol and systemic propranolol therapy, safety and monitoring guidelines, and strategies for preventing visual complications and post-treatment recurrence.

Methodology

To capture and critically evaluate the complex interplay between pediatric soft-tissue diagnostic imaging, ophthalmic complication risks, and pharmacological beta-blocker management of periocular infantile hemangiomas, this narrative review employed a multidisciplinary literature synthesis across pediatric dermatology, clinical ophthalmology, pediatric surgery, vascular anomalies, and pharmacological therapeutics. The investigative timeline was strategically bounded between 2016 and 2026 to ensure that synthesized empirical evidence captures contemporary diagnostic ultrasound protocols, standardized oral propranolol titration guidelines, topical timolol administration models, and long-term risk assessment frameworks. Early foundational publications were selectively retained only when they provided essential theoretical concepts necessary for interpreting the natural biological cycle of vascular tumors and the historical shift in medical management.

Search Strategy and Information Sources

Information retrieval was executed across major international biomedical databases: PubMed, MEDLINE, EMBASE, Google Scholar, and the Cochrane Database of Systematic Reviews. The electronic search strategy incorporated targeted, Boolean-linked keyword strings designed to capture the intersection of periocular infantile hemangiomas, ophthalmic risk assessment, and conservative beta-blocker therapy, including:

- ("infantile hemangioma" OR "periocular hemangioma" OR "capillary hemangioma") AND ("propranolol" OR "timolol" OR "beta-blocker therapy")
- ("ultrasound" OR "color Doppler" OR "soft-tissue imaging") AND ("diagnostic dynamics" OR "volumetric growth" OR "vascularity")
- ("amblyopia" OR "astigmatism" OR "visual axis obstruction" OR "ptosis") AND ("periocular region" OR "ocular complications")
- ("propranolol dosing" OR "dose titration" OR "adverse events" OR "rebound growth") AND ("pediatric vascular tumors" OR "infantile hemangiomas")
- ("ISSVA classification" OR "vascular anomalies" OR "spontaneous involution") AND ("clinical guidelines" OR "consensus statements")

Inclusion and Exclusion Criteria

Retrieved publications were screened and deemed eligible for inclusion if they satisfied at least one of the following operational inclusion criteria:

1. Evaluated clinical presentation, ultrasound characteristics, dynamic volumetric progression, or color Doppler vascularity specifically in pediatric populations with periocular or facial infantile hemangiomas;
2. Examined ophthalmic sequelae, functional risks, structural visual axis threats (such as astigmatism, ptosis, or amblyopia), or pre-treatment ophthalmological screening protocols;
3. Investigated pharmacological mechanisms, systemic propranolol dosing schedules (typically titrated up to 2–3 mg/kg/day), topical timolol application schemes, or safety and monitoring protocols;
4. Documented long-term treatment outcomes, regression rates, post-treatment rebound growth, or long-term follow-up findings following beta-blocker cessation.

Conversely, publications were systematically excluded if they met any of the following criteria:

1. Did not directly address vascular anomalies, infantile hemangiomas, pediatric ophthalmology, or beta-blocker pharmacotherapy;
2. Evaluated adult vascular lesions, congenital hemangiomas (e.g., RICH or NICH), or high-flow vascular malformations (such as arteriovenous malformations) lacking the typical infantile proliferative phase;
3. Consisted of commercial product marketing, non-refereed medical blogs, popular media articles, or opinion-based commentary lacking structured empirical clinical data;
4. Manuscripts without available full English text.

Finally, investigations focusing solely on systemic surgical resections, invasive sclerotherapy without prior medical therapy, or systemic corticosteroid protocols without reference to modern beta-blocker standards were kept outside the primary scope of this review. The risk-benefit profiles, complication rates, and treatment guidelines of historical invasive or corticosteroid-based interventions lack the safety metrics and targeted efficacy characteristic of contemporary pediatric vascular tumor management.

Results

Diagnostic Evolution and Ultrasonographic Dynamics

The diagnostic trajectory of periocular infantile hemangiomas (IHs) during early infancy is frequently marked by diagnostic uncertainty, particularly when lesions present with a predominantly deep subcutaneous component (Ginguerra et al., 2018; Kutz et al., 2015). Initial cutaneous manifestations often appear as subtle erythema or non-specific periorbital swelling that can be clinically misdiagnosed as post-traumatic hematomas, venous malformations, or deep soft-tissue masses (Goldenberg et al., 2025; Kutz et al., 2015).

High-resolution ultrasonography paired with color Doppler imaging serves as the primary non-invasive modality for capturing the rapid volumetric expansion characteristic of the proliferative phase (Kutz et al., 2015; Zhao et al., 2011). Early ultrasound examinations during the initial weeks of proliferation may display irregular subcutaneous hypoechoic structures with minimal or undetectable vascular signals (Ginguerra et al., 2018). However, follow-up ultrasonography performed within 4 to 8 weeks typically demonstrates dramatic growth—frequently revealing a multi-fold increase in linear and volumetric dimensions alongside high peak systolic Doppler velocities and dense internal vascularity (Ginguerra et al., 2018; Kutz et al., 2015). Serial Doppler monitoring effectively captures the transition from aggressive endothelial proliferation to drug-induced vascular stasis and eventual structural involution (Kutz et al., 2015).

Ophthalmic Complications and Visual Risk Stratification

Periocular location places infants at high risk for secondary visual impairment due to mechanical displacement of surrounding adnexal structures (Al-Haddad et al., 2019; Samuelov et al., 2018; Zhao et al., 2019). Clinical outcome data highlight several distinct structural risks:

- **Mechanical Ptosis and Visual Axis Occlusion:** Upper eyelid involvement directly threatens visual acuity by physically obscuring the pupil, leading to rapid deprivation amblyopia if the obstruction persists during early visual development (Herlihy et al., 2016; Samuelov et al., 2018).
- **Corneal Distortion and Induced Astigmatism:** Direct mass effect from lesions situated in the eyelid or periorbital soft tissues exerts asymmetrical focal pressure on the globe (Herlihy et al., 2016). This biomechanical compression alters corneal steepness, resulting in high astigmatism and refractive anisometropia (Al-Haddad et al., 2019; Herlihy et al., 2016).
- **Proptosis and Ocular Motility Restriction:** Retrobulbar or deep orbital extension induces forward displacement of the eye (proptosis) and localized restriction of extraocular muscle dynamics (Ginguerra et al., 2018; Zhao et al., 2019).

Comparative risk analyses indicate that hemangiomas larger than 10 mm in diameter, mixed/deep subtype lesions, and those involving the upper eyelid or medial canthus carry significantly higher odds of inducing severe ocular sequelae compared to small, localized superficial lesions (Samuelov et al., 2018; Zhao et al., 2019).

Pharmacological Efficacy of Systemic and Topical beta-Blockers

The clinical literature demonstrates robust therapeutic efficacy for beta-adrenergic receptor antagonists in regressing periocular infantile hemangiomas (Léauté-Labrèze et al., 2015; Tran et al., 2016).

- **Systemic Oral Propranolol:** As established by clinical practice guidelines, oral propranolol titrated to a target maintenance dose of 2 to 3 mg/kg/day (administered in divided doses) represents the first-line gold standard for problematic periocular IHs (Krowchuk et al., 2019; Léauté-Labrèze et al., 2015; Smithson et al., 2017). Initiating oral therapy induces rapid softening, lightening of cutaneous color, and volumetric shrinkage of the deep subcutaneous mass within the first 4 to 8 weeks of treatment (Ginguerra et al., 2018; Malvindi et al., 2025). Complete or near-complete clearing of the deep component is documented via ultrasonography following 6 to 9 months of continuous therapy (Ginguerra et al., 2018; Zhao et al., 2011).
- **Topical Timolol Maleate:** Topical 0.5% timolol maleate drops or gel applied directly to the cutaneous surface provide a targeted therapeutic option for thin, superficial lesions (< 1 to 2 mm in thickness) (Han et al., 2024; Ye et al., 2012). While topical administration minimizes systemic adverse events, evidence shows its transdermal tissue penetration is insufficient to control large subcutaneous or orbital components (Han et al., 2024; Qiao et al., 2020).
- **Combination and Alternative Regimens:** Multicenter trials and meta-analyses show that combining low-dose oral propranolol with adjunct topical timolol can accelerate superficial color clearance without increasing systemic toxicity (Qiao et al., 2020). Selective beta-adrenergic blockers, such as oral atenolol, demonstrate comparable efficacy in reducing tumor volume while exhibiting favorable central nervous system safety profiles (Baruch et al., 2024; Ji et al., 2021).

Safety Profiles and Rebound Growth Rates

Systemic oral propranolol exhibits an acceptable pediatric safety profile when managed with baseline screening and appropriate caregiver education (Adams & Ryan, 2022; Krowchuk et al., 2019). Commonly reported pharmacological side effects include transient bradycardia, asymptomatic hypotension, cold extremities, sleep disturbances, and rare hypoglycemic events during periods of reduced oral intake (Adams & Ryan, 2022; Ghahvehchian et al., 2024).

Post-treatment rebound growth remains a recognized clinical phenomenon following the tapering or cessation of beta-blocker therapy (Gong et al., 2025; Shah et al., 2016). Meta-analytic data indicate that secondary proliferation occurs in approximately 10% to 25% of treated infants (Gong et al., 2025; Shah et al., 2016). Significant risk factors associated with post-treatment recurrence include:

1. Early treatment discontinuation prior to 12 months of age (Gong et al., 2025; Shah et al., 2016);
2. Presence of a substantial deep subcutaneous or mixed-type anatomical component (Baruch et al., 2024; Shah et al., 2016);
3. Rapid dose tapering schedules without sufficient post-discontinuation monitoring (Gong et al., 2025; Shah et al., 2016).

Long-term prospective follow-up studies confirm that most rebound cases respond successfully to a second course of oral propranolol or temporary reinstatement of topical timolol, achieving stable long-term visual and aesthetic outcomes (Ghahvehchian et al., 2024; Shah et al., 2016).

Longitudinal Refractive and Visual Acuity Stabilization

Longitudinal visual outcome assessments demonstrate that prompt initiation of systemic beta-blocker therapy directly correlates with the stabilization and partial reversal of hemangioma-induced refractive errors (Herlihy et al., 2016; Zhao et al., 2019). Quantitative retinoscopy performed before and after oral propranolol administration reveals a statistically significant reduction in cylinder power (astigmatism) as tumor regression reduces localized pressure on the cornea (Al-Haddad et al., 2019; Herlihy et al., 2016). Furthermore, early pharmacological clearance of upper eyelid lesions prevents long-term deprivation amblyopia, allowing infants to regain symmetrical binocular visual acuity (Herlihy et al., 2016; Zhao et al., 2019). Comparative longitudinal studies indicate that infants treated with oral propranolol during the early proliferative window achieve significantly superior visual acuity outcomes compared to historical controls managed with intralesional corticosteroid injections or conservative observation (Herlihy et al., 2016; Tran et al., 2016).

Comparative Analysis of Pharmacological Modalities

Systematic evaluations comparing mono-therapeutic regimens confirm distinct operational indicators for topical versus systemic agents (Han et al., 2024; Hu et al., 2026). Meta-analytic synthesis demonstrates that while topical 0.5% timolol maleate achieves equivalent regression rates to oral propranolol in purely superficial lesions (< 2 mm in thickness), systemic propranolol exhibits overwhelming superiority in overall response rate, rate of volumetric reduction, and resolution of structural tissue distortion in mixed and deep subtypes (Han et al., 2024; Hu et al., 2026; Qiao et al., 2020). Additionally, comparative clinical trials assessing alternative oral agents show that selective beta-1-antagonists (such as atenolol) yield clinical resolution rates (85%–92%) comparable to non-selective propranolol while demonstrating a reduced incidence of bronchial reactivity and central sleep disruptions (Baruch et al., 2024; Ji et al., 2021).

Multidisciplinary Care Pathways and Surgical Adjuncts

Structured multidisciplinary protocols—integrating pediatric dermatology, pediatric ophthalmology, and pediatric surgery—consistently achieve optimal therapeutic outcomes while minimizing unnecessary invasive procedures (Krowchuk et al., 2019; Mazhar et al., 2020; Smithson et al., 2017). With the widespread adoption of first-line beta-blocker pharmacotherapy, the requirement for early surgical debulking or invasive intralesional steroid injections has decreased dramatically (Lopez-Gutierrez, 2015; Macca et al., 2022). Surgical intervention is now primarily reserved for secondary procedures, such as the excision of minor post-involution residual fibrofatty tissue pads or corrective eyelid plastic surgery in severe long-standing ptosis (Ghahvehchian et al., 2024; Mazhar et al., 2020). Collaborative care pathways incorporating serial retinoscopy, regular pediatric monitoring, and standardized ultrasound follow-up ensure maximum visual protection and long-term aesthetic restoration (Krowchuk et al., 2019; Smithson et al., 2017).

Discussion

The synthesis of contemporary clinical literature highlights a profound evolution in the diagnostic and therapeutic management of periocular infantile hemangiomas (IHs) over the past decade. Historically managed with high-dose systemic corticosteroids, intralesional steroid injections, or early surgical intervention, periocular vascular tumors are now treated via targeted pharmacotherapy and high-resolution imaging protocols (Krowchuk et al., 2019; Léauté-Labrèze et al., 2015; Macca et al., 2022). Nevertheless, the delicate anatomical location of periocular lesions presents unique challenges regarding early diagnostic precision, amblyopia risk management, treatment duration optimization, and post-cessation rebound mitigation (Al-Haddad et al., 2019; Shah et al., 2016; Zhao et al., 2019).

Diagnostic Challenges and the Crucial Role of Ultrasonography

A central insight gained from empirical evaluations is the diagnostic ambiguity inherent to the early proliferative phase of periocular IHs (Ginguerra et al., 2018; Kutz et al., 2015). Because deep subcutaneous lesions often present without classic cutaneous involvement or telangiectasia, initial clinical presentations are easily confounded with soft-tissue neoplasms, vascular malformations, or deep post-traumatic hematomas (Goldenberg et al., 2025; Kutz et al., 2015). Misdiagnosis or delayed diagnosis during the rapid proliferative window (typically between 1 and 4 months of age) increases the incidence of secondary refractive amblyopia (Samuelov et al., 2018; Zhao et al., 2019).

High-resolution ultrasonography paired with color Doppler imaging bridges this diagnostic gap (Kutz et al., 2015; Zhao et al., 2011). Serial ultrasound monitoring provides an objective quantitative metric for evaluating structural response to beta-blocker therapy, capturing decreases in lesional depth, tissue density, and peak systolic velocity long before significant cutaneous alteration is visible (Ginguerra et al., 2018; Kutz et al., 2015). Relying solely on superficial physical inspection can be misleading, as cutaneous clearance may obscure persistent deep subcutaneous activity, increasing the risk of premature drug cessation (Ginguerra et al., 2018; Shah et al., 2016). Therefore, incorporating standardized serial Doppler follow-up into initial pediatric workflows is essential for guiding accurate dosing decisions and determining the appropriate timing for treatment tapering (Kutz et al., 2015; Smithson et al., 2017).

Biomechanical Mechanisms of Visual Impairment

The anatomical location of periocular hemangiomas dictates their clinical severity (Al-Haddad et al., 2019; Tran et al., 2016). The primary mechanisms of ocular morbidity—mechanical ptosis, visual axis occlusion, and induced astigmatism—are directly linked to mass effect on the globe and eyelid structures (Herlihy et al., 2016; Samuelov et al., 2018). As asymmetrical compression alters corneal curvature, high refractive cylinder errors develop rapidly (Herlihy et al., 2016). The early critical period of visual development means that even brief periods of visual axis occlusion or severe uncorrected anisometropia can result in permanent deprivation or refractive amblyopia (Herlihy et al., 2016; Zhao et al., 2019).

Prompt intervention with systemic oral propranolol mitigates these structural risks by rapidly inducing localized vasoconstriction, down-regulating pro-angiogenic signals (such as VEGF and bFGF), and promoting endothelial cell apoptosis (Storch & Hoeger, 2010). Clinical outcome data confirm that swift volumetric reduction directly relieves focal pressure on the cornea, leading to measurable reductions in astigmatic error and the preservation of symmetrical visual acuity (Al-Haddad et al., 2019; Herlihy et al., 2016).

Molecular Pathways and Potential Biomarker Integration

Expanding the theoretical understanding of pharmacological intervention requires evaluating the underlying cellular pathways modulated by beta-adrenergic antagonists (Storch & Hoeger, 2010). Beyond immediate hemodynamic vasoconstriction, long-term regression induced by oral propranolol is mediated via down-regulation of the hypoxia-inducible factor 1-alfa (HIF-1-alfa) and vascular endothelial growth factor (VEGF) signaling cascades, alongside the activation of intrinsic apoptotic pathways within proliferating endothelial cells (Storch & Hoeger, 2010). Emerging clinical investigations highlight the prospective utility of monitoring serum VEGF levels or specific endothelial biomarkers in parallel with color Doppler ultrasonography to quantify biological tumor activity (Kutz et al., 2015; Storch & Hoeger, 2010). Integrating molecular profiling with serial hemodynamic ultrasound parameter tracking could refine clinical risk stratification, enabling precise, patient-tailored dosing protocols that minimize exposure while preventing sub-clinical endothelial reactivation (Gong et al., 2025; Kutz et al., 2015).

Comparative Pharmacotherapy: Oral Propranolol, Topical Timolol, and Atenolol

Selecting the optimal pharmacological regimen requires balancing therapeutic efficacy against systemic exposure and safety (Hu et al., 2026; Krowchuk et al., 2019). Oral propranolol remains the undisputed gold-standard therapy for problematic periocular IHs due to its proven capacity to penetrate deep orbital soft tissues and regress mixed/deep subcutaneous masses (Léauté-Labrèze et al., 2015; Malvindi et al., 2025).

Topical 0.5% timolol maleate has established itself as an effective, highly targeted alternative specifically for superficial, thin (< 1–2 mm) cutaneous hemangiomas (Han et al., 2024; Ye et al., 2012). It provides excellent local control while significantly minimizing the risk of systemic adverse events such as hypoglycemia, bradycardia, or bronchospasm (Adams & Ryan, 2022; Han et al., 2024). However, evidence synthesized across systematic reviews demonstrates that topical timolol lacks sufficient transdermal penetration to manage deep subcutaneous components or large mixed lesions (Han et al., 2024; Qiao et al., 2020). Attempting mono-therapy with topical agents for high-risk periocular lesions with deep involvement risks under-treating the tumor and allowing irreversible visual impairment to progress (Han et al., 2024; Samuelov et al., 2018).

Recent evidence also supports the efficacy of combination therapies and alternative oral beta-blockers (Ji et al., 2021; Qiao et al., 2020). Concurrent administration of low-dose oral propranolol and topical timolol offers a synergistic effect, rapidly clearing superficial erythema while controlling deep tumor proliferation (Qiao et al., 2020). Moreover, selective beta-adrenergic blockers like oral atenolol demonstrate comparable tumor regression rates (85%–92%) with a lower incidence of lipophilic central nervous system side effects (such as sleep disruption and restlessness) (Baruch et al., 2024; Ji et al., 2021). While atenolol presents a promising alternative for infants sensitive to propranolol-induced side effects, non-selective oral propranolol remains the primary benchmark in pediatric consensus pathways (Hu et al., 2026; Krowchuk et al., 2019).

Managing Rebound Growth and Long-Term Outcomes

Post-treatment rebound growth remains one of the most significant management challenges following beta-blocker cessation (Gong et al., 2025; Shah et al., 2016). Occurring in approximately 10% to 25% of cases, secondary proliferation typically manifests when treatment is discontinued prematurely before the end of the natural proliferative phase—typically prior to 12 months of age (Gong et al., 2025; Shah et al., 2016). Deep subcutaneous and mixed-type lesions carry a heightened baseline risk for recurrence (Baruch et al., 2024; Shah et al., 2016).

Preventing rebound growth requires maintaining maintenance beta-blocker therapy until vascular maturation and true quiescence are confirmed (Gong et al., 2025; Shah et al., 2016). Utilizing serial Doppler ultrasonography during the drug-tapering phase helps ensure that sub-clinical subcutaneous proliferation has ceased prior to complete drug withdrawal (Ginguerra et al., 2018; Kutz et al., 2015). When rebound growth does occur, re-instituting a secondary course of oral propranolol or temporary topical timolol reliably restores lesional control without compromising long-term aesthetic or visual outcomes (Ghahvehchian et al., 2024; Shah et al., 2016).

Psychosocial Impact and Aesthetic Rehabilitation

In addition to preserving visual acuity, the rapid resolution of facial and periocular lesions carries profound psychosocial implications for early child development and family dynamics (Adams & Ryan, 2022; Krowchuk et al., 2019). Prominent facial vascular anomalies frequently induce significant parental anxiety and emotional stress during the infant's first months of life (Adams & Ryan, 2022; Zhao et al., 2019). Pharmacological therapy with oral propranolol or topical timolol not only reverses visual-axis threats but also dramatically accelerates cutaneous clearing, preventing severe persistent tissue distortion or residual skin laxity (Han et al., 2024; Herlihy et al., 2016). Early intervention limits the necessity for complex reconstructive plastic surgery in later childhood, thereby alleviating long-term psychosocial burden and ensuring favorable structural and aesthetic outcomes (Lopez-Gutierrez, 2015; Mazhar et al., 2020; Smithson et al., 2017).

Multidisciplinary Care Model and Clinical Implications

The management of periocular infantile hemangiomas necessitates a collaborative, multidisciplinary framework involving pediatric dermatologists, pediatric ophthalmologists, pediatric surgeons, and radiodiagnostic specialists (Krowchuk et al., 2019; Mazhar et al., 2020; Smithson et al., 2017). Baseline visual axis assessment, refraction, and orthoptic evaluation should be paired with immediate pharmacological initiation upon detecting visual threat (Al-Haddad et al., 2019; Herlihy et al., 2016). While medical management has drastically reduced the need for early surgical intervention, minor secondary reconstructive procedures—such as the excision of residual fibrofatty tissue or corrective eyelid surgery for persistent skin laxity—remain valuable adjuncts following drug-induced involution (Lopez-Gutierrez, 2015; Mazhar et al., 2020).

Limitations and Future Directions

While current evidence strongly supports early beta-blocker intervention, several limitations in the literature persist. Variability in treatment duration, non-standardized tapering protocols across clinical centers, and a scarcity of long-term prospective comparative trials evaluating oral atenolol versus propranolol in periocular-specific cohorts highlight the need for further research (Baruch et al., 2024; Ji et al., 2021). Future randomized controlled studies should focus on establishing standardized, ultrasound-guided criteria for treatment discontinuation and refining personalized dosing algorithms to optimize both visual safety and long-term therapeutic durability (Gong et al., 2025; Kutz et al., 2015).

Conclusions

Periocular infantile hemangiomas represent a high-risk clinical subset of pediatric vascular anomalies that demand early diagnostic precision and prompt therapeutic management. The anatomical proximity of these proliferating endothelial tumors to the developing visual axis creates a immediate risk of severe ocular morbidities—most notably mechanical ptosis, induced astigmatism, refractive anisometropia, and permanent deprivation amblyopia (Herlihy et al., 2016; Samuelov et al., 2018; Zhao et al., 2019).

The clinical paradigm shift toward pharmacotherapy with beta-adrenergic receptor antagonists has transformed patient outcomes (Léauté-Labrèze et al., 2015). Oral propranolol remains the established gold-standard treatment for problematic periocular lesions with deep subcutaneous or retrobulbar extension, consistently demonstrating superior volumetric reduction, rapid reversal of structural tissue displacement, and high rates of visual axis stabilization (Krowchuk et al., 2019; Malvindi et al., 2025). Topical 0.5% timolol maleate offers a targeted, highly safe modality reserved strictly for thin, superficial cutaneous lesions (< 1–2 mm), though it lacks the tissue penetration required for complex mixed or deep sub-types (Han et al., 2024; Ye et al., 2012). Alternative systemic agents, such as selective beta-1-antagonists (oral atenolol), present viable options with favorable central nervous system safety profiles (Baruch et al., 2024; Ji et al., 2021).

To optimize long-term visual and aesthetic outcomes while minimizing post-treatment rebound growth, clinical care must adhere to three core principles:

1. **Early Diagnostic Imaging:** Serial high-resolution ultrasonography paired with color Doppler imaging should be integrated into baseline evaluations to delineate deep subcutaneous involvement and establish quantitative hemodynamic parameters (Kutz et al., 2015; Zhao et al., 2011).
2. **Objective Monitoring and Tapering:** Pharmacological treatment should be maintained throughout the active proliferative window (typically until 12 months of age or older), using Doppler ultrasound parameters alongside cutaneous appearance to guide treatment tapering and prevent sub-clinical recurrence (Ginguerra et al., 2018; Gong et al., 2025; Shah et al., 2016).
3. **Multidisciplinary Collaboration:** A unified care model joining pediatric dermatologists, pediatric ophthalmologists, and pediatric surgeons is essential for continuous orthoptic tracking, early amblyopia management, and secondary reconstructive planning when necessary (Krowchuk et al., 2019; Mazhar et al., 2020; Smithson et al., 2017).

Future clinical research should prioritize standardized, multi-center trials focused on defining precise, biomarker- and ultrasound-guided criteria for treatment discontinuation, alongside prospective comparisons of novel beta-blocker protocols to continuously refine visual safety and therapeutic durability in pediatric patients.

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