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ORIGINAL RESEARCH

Additive Therapeutic Effects of Topical Sirolimus Following Oral Propranolol Therapy for Kaposiform Hemangioendothelioma

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Background: Kaposiform hemangioendothelioma (KHE) is a rare but aggressive vascular tumor, potentially life-threatening when associated with Kasabach-Merritt phenomenon (KMP). Oral sirolimus is effective but may cause systemic adverse effects in infants. Oral propranolol offers a safer alternative in early infancy, but its efficacy may plateau over time. Sequential topical sirolimus may enhance outcomes while minimizing systemic toxicity.

Objective: To evaluate the additive therapeutic effect and safety of topical sirolimus in KHE patients with suboptimal response after oral propranolol.

Methods: This retrospective study included five pediatric patients with cutaneous KHE treated at Beijing Children's Hospital from October 2018 to October 2022. All had received oral propranolol for ≥24 months and showed therapeutic plateau (tumor shrinkage ≤70%). They were subsequently treated with 0.1% topical sirolimus ointment twice daily for at least six months and followed for one year. Efficacy was assessed by Visual Analog Scale (VAS), Doppler ultrasound, and a four-grade evaluation system; safety was monitored throughout.

Results: All patients showed significant improvement within 6–12 months (mean: 9.6 months), achieving Grade III or IV response. Doppler imaging revealed reduced or absent blood flow signals, and lesions nearly regressed in some cases. Symptoms such as pain and localized hyperthermia resolved, and skin appearance normalized. Two patients experienced mild local irritation; no systemic adverse effects or recurrences were observed.

Conclusion: Sequential topical sirolimus following oral propranolol offers a safe and effective treatment strategy for KHE, especially after therapeutic plateau. It enhances efficacy, avoids systemic toxicity, and may accelerate lesion regression. Further large-scale studies are warranted to optimize individualized treatment protocols.

Keywords: kaposiform hemangioendothelioma, KHE, sirolimus, propranolol, topical therapy, sequential therapy, pediatric vascular tumor

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor characterized by the proliferation of spindle-shaped cells and the formation of slit-like vascular channels. It primarily affects infants and young children, commonly involving the extremities, trunk, and head and neck regions. Clinically, KHE typically presents as a rapidly enlarging mass accompanied by skin discoloration and pain. Diagnosis relies primarily on histopathological examination, with careful differentiation from other vascular tumors. The treatment of KHE remains challenging. Although surgical excision is considered the first-line approach, complete resection is often difficult due to the tumor's location and extent. Moreover, KHE may be complicated by Kasabach-Merritt phenomenon (KMP), a life-threatening coagulopathy that further complicates management.[1] Therefore, exploring effective pharmacologic strategies is essential to improving outcomes in patients with KHE.

Propranolol, a non-selective β-adrenergic receptor blocker, has recently gained attention for its anti-angiogenic properties. Clinical studies have reported that oral propranolol achieves a response rate of 50–80% in the treatment of KHE, significantly

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improving patient prognosis.[2] However, propranolol monotherapy has limitations. Some patients demonstrate suboptimal response, and prolonged administration may lead to adverse events such as bradycardia and hypotension. In addition, propranolol shows limited efficacy in treating deep-seated or visceral lesions. These limitations have prompted the investigation of sequential or combination therapeutic strategies to enhance clinical efficacy.

Sirolimus is a macrolide immunosuppressant that exerts anti-tumor effects by inhibiting the mechanistic target of rapamycin (mTOR) signaling pathway. Its therapeutic mechanisms include inhibition of angiogenesis, induction of tumor cell apoptosis, and modulation of immune responses. In KHE treatment, topical sirolimus allows direct application to the lesion, achieving high local drug concentrations while minimizing systemic adverse effects. Clinical evidence supports the safety and efficacy of topical sirolimus in pediatric patients with KHE.[3,4]

Given the distinct mechanisms of action of sirolimus and propranolol, a sequential treatment strategy has been proposed. Investigating the additive therapeutic effect of topical sirolimus following oral propranolol may provide valuable clinical evidence for optimizing treatment protocols in the management of KHE.[5]

Materials and Methods

This study was a single-center, retrospective, multi-case analysis involving pediatric patients from the Department of Dermatology at Beijing Children's Hospital. The aim was to evaluate the clinical efficacy of topical sirolimus following treatment stagnation with oral propranolol in patients with KHE. The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, and written informed consent was obtained from the legal guardians of all patients. Consent was also obtained for the medical use and archival of clinical photographs. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Patient Clinical Data

In this retrospective observational study, data were collected from patients who received topical sirolimus treatment after discontinuation of oral propranolol at the Dermatology Outpatient Clinic of Beijing Children's Hospital between October 2018 and October 2022. A total of five pediatric patients (three males and two females) were included. The age of disease onset ranged from birth to 2 months, and topical sirolimus therapy was initiated between 27 and 46 months of age. Lesion sites included the left thigh, left buttock, right shoulder, and left ear, with tumor sizes ranging from 20.64 cm^2 to 195 cm^2.

Inclusion Criteria

(1) Cutaneous KHE diagnosed according to the 2018 classification criteria of the International Society for the Study of Vascular Anomalies (ISSVA). (2) Diagnosis confirmed by ultrasound and histopathology, including typical immunohistochemical markers: D2-40(+), CD31(+), CD34(+), VEGFR-3(+), and GLUT-1(+). (3) Prior treatment with oral propranolol for ≥24 months, with disease stabilization defined as tumor shrinkage ≤70% and no further improvement. (4) No severe comorbidities or contraindications to sirolimus. (5) Exclusion of patients with concurrent vascular anomalies or malignancies. (6) Exclusion of patients with a history of systemic sirolimus therapy. (7) Exclusion of patients with KHE complicated by Kasabach-Merritt phenomenon (KMP).

Therapy

Following caregiver training, 0.1% topical sirolimus cream was applied to the entire lesion area twice daily, ensuring full coverage. The minimum treatment duration was six months, followed by a one-year follow-up period after discontinuation. If significant erythema, swelling, or ulceration occurred during treatment, mupirocin ointment was prescribed. If symptoms did not improve within one week, the application frequency was reduced to once daily. If symptoms persisted beyond two weeks, topical sirolimus was temporarily discontinued.

Efficacy Criteria and Methods

Standardized photographs were taken before each treatment session using the same camera, settings, and angles to ensure consistency. Lesion color and size changes were assessed in person by a dermatologist based on the patient's

clinical presentation. Tumor size and thickness were evaluated using the VAS and localized B-mode ultrasound, compared with baseline measurements. Treatment efficacy was determined according to the four-grade system proposed by Achauer et al[6] :Grade I: 0–25% tumor reduction or mild lightening of lesion color compared to baseline; Grade II: 26–50% tumor reduction or noticeable lightening of lesion color; Grade III: 51–75% tumor reduction with significant lightening of lesion color; Grade IV: >75% tumor reduction or complete normalization of skin color. The treatment efficacy rate was calculated as follows: (Number of patients with a Grade II–IV response / Total number of patients) × 100%. Patients were followed up every three months, including measurement of lesion area and blood flow (via B-mode ultrasound), symptom evaluation (eg, color changes, induration, and pain), and monitoring for adverse effects. Safety assessments included local skin reactions (erythema, swelling), routine blood and urine tests, liver and renal function tests, and coagulation profiles. The primary endpoints were the occurrence of KMP and achievement of Grade IV response. Secondary endpoints included drug safety and tolerability. Recorded adverse effects included mild local skin irritation, hepatic or renal dysfunction, and coagulation abnormalities.

Statistical Analysis

Data were analyzed using SPSS software version 27.0. Descriptive statistics were used for continuous variables, which were reported as mean, median, minimum, and maximum values. Categorical variables were expressed as frequencies and percentages.

Results

This study analyzed clinical treatment outcomes from five pediatric patients diagnosed with KHE. By evaluating the therapeutic efficacy, safety, and adverse reactions of topical sirolimus cream, the findings offer important insights for optimizing comprehensive KHE management (see Table 1).

Therapeutic Efficacy

The duration of topical sirolimus therapy among the five patients ranged from 6 to 27 months, with a mean duration of 13.4 months. Following oral propranolol treatment, the therapeutic responses were Grade I in one patient, Grade II in one patient, and Grade III in three patients. After the addition of topical sirolimus, all five patients achieved a Grade IV response, indicating a significant improvement in clinical efficacy (Figures 1 and 2).

Prior to treatment, the lesions appeared as firm, palpable masses. After therapy, the masses gradually softened and regressed, leaving only faint erythema on the skin surface, with both appearance and texture nearly returning to normal. Among these cases, two patients experienced complete resolution of pre-treatment tenderness, and one patient with localized skin warmth showed full remission. Additionally, three patients demonstrated progressive fading of erythema to near-normal skin tone, and one patient with mild epidermal thickening exhibited marked improvement post-treatment.

Before treatment, Doppler ultrasound revealed abundant or slightly increased blood flow signals in the lesion areas. After treatment, these signals were significantly reduced or completely disappeared. In some cases, previously ill-defined lesions or detectable tumor masses became undetectable Notably, in patients with larger lesions, a marked reduction in blood supply was observed, along with gradual tissue shrinkage and normalization of lesion characteristics (Table 1).

Adverse Reactions

No patients discontinued treatment due to adverse effects. Two patients (40%) experienced mild local skin irritation, including erythema and pruritus, during the early phase of treatment. These symptoms resolved completely following symptomatic management and adjustment of application frequency, without affecting the final therapeutic outcome. Routine blood and urine tests, liver and renal function assessments, and coagulation profiles were performed regularly during treatment, with no abnormalities observed in any of the patients.

Table 1 Clinical Characteristics and Treatment Outcomes of KHE Patients Treated with Propranolol and Sirolimus

Case Number	Age of Onset (months)	Age at Treatment Initiation (months)	Sex	Lesion Location	Pre-Treatment Tumor Area (cm^2)	Pre-Treatment Tumor Thickness (cm)	Pre-Treatment Ultrasound Findings	Tumor Area After Propranolol Discontinuation (cm^2)	Tumor Thickness After Propranolol Discontinuation (cm)	Ultrasound Findings After Propranolol Discontinuation	Tumor Area After Sirolimus Discontinuation (cm^2)	Tumor Thickness After Sirolimus Discontinuation (cm)	Ultrasound Findings After Sirolimus Discontinuation	Duration of Oral Propranolol Therapy (months)	Oral Propranolol Treatment Efficacy	Duration of Topical Sirolimus Treatment (months)	Final Efficacy
1	1	31	Male	Left thigh	20.64	1.5	Rich blood flow signals	6.21	0.4	Slightly increased blood flow signals	Unclear boundaries	0	No significant increase in blood flow signals	46	III	12	IV
2	2	46	Female	Left buttock	88	2.1	Slightly rich blood flow signals	32	0.5	Slightly increased blood flow signals	20.8	0.3	No significant blood flow signals	40	III	10	IV
3	0	35	Male	Left thigh	195	2.4	Rich blood flow signals	107.25	1.8	Rich vascular signals	51.5	0.2	No significant blood flow signals	42	II	6	IV
4	2	27	Female	Right shoulder	52	1.7	Rich blood flow signals	40.5	1.4	Rich vascular signals	Unclear boundaries	0	No significant increase in blood flow signals	24	I	27	IV
5	1	32	Male	Left ear	20.1	0.8	Rich blood flow signals	5.7	0.5	Slightly increased blood flow signals	Unclear boundaries	0	No significant blood flow signals	33	III	12	IV

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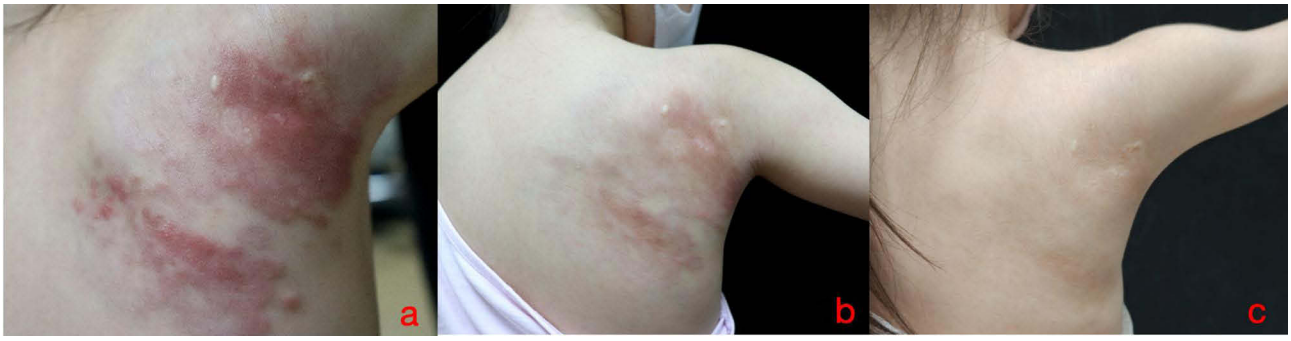

Figure 1 (**a**) Baseline presentation prior to oral propranolol therapy, showing a prominent cutaneous lesion with erythema, localized swelling, and a palpable subcutaneous mass. The lesion exhibited characteristic features of KHE, including prominent vascularity and firm texture on palpation. (**b**) Demonstrates a Grade II regression of KHE following oral propranolol treatment. The lesion showed reduced volume, partial resolution of erythema and swelling, improved skin texture, and mild residual hyperpigmentation. Doppler ultrasound revealed persistent blood flow signals, suggesting residual tumor tissue, consistent with a Grade II response based on the four-grade evaluation system. (**c**) Clinical appearance after 27 months of topical sirolimus therapy, showing near-complete lesion involution. Doppler ultrasound revealed no evidence of residual vascular proliferation.

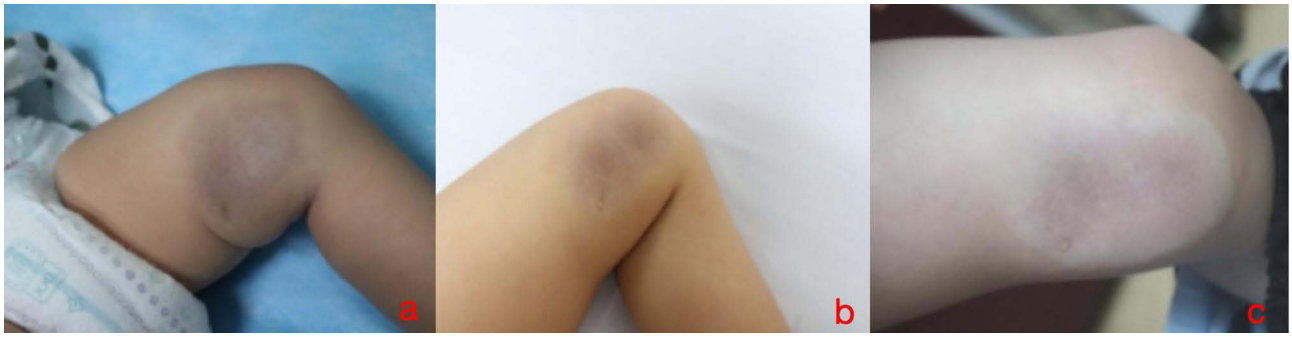

Figure 2 (**a**) A well-circumscribed, firm, violaceous subcutaneous mass was observed on the knee, accompanied by mild swelling. The lesion was tender on palpation, with localized warmth and restricted mobility. (**b**) After 46 months of oral propranolol therapy, the lesion showed significant reduction in size and vascular congestion, with diminished violaceous discoloration. Post-inflammatory hyperpigmentation and residual skin thickening persisted. Mobility restriction partially improved, and the mass softened. However, a therapeutic plateau was evident, with Doppler ultrasound revealing a large residual mass and abundant blood flow. (**c**) Following 12 months of topical sirolimus therapy, the lesion demonstrated marked regression, with substantial softening of the subcutaneous mass. There was no tenderness, localized warmth, or mobility restriction, indicating effective lesion control. The condition remained stable during the one-year follow-up period.

Recurrence and Follow-Up

During the follow-up period, no lesion recurrence was observed in any of the patients. The treated areas continued to improve, and skin appearance gradually returned to normal. All families reported high satisfaction with the treatment outcome, describing the topical regimen as convenient and effective.

Comprehensive Efficacy Evaluation

Topical sirolimus cream significantly enhanced treatment outcomes in KHE patients who had reached a therapeutic plateau with oral propranolol. All patients ultimately achieved a Grade IV tumor response, with no lesion recurrence observed during the follow-up period. These results suggest a durable clinical benefit and high treatment adherence. No cases of Kasabach-Merritt phenomenon were observed during treatment with either oral propranolol or topical sirolimus.

Discussion

KHE is a rare and complex vascular tumor, and its treatment strategies continue to pose significant challenges. In recent years, with advancements in molecular mechanism research, targeted therapy has gradually become the preferred treatment option for KHE. Sirolimus, by inhibiting the mTOR signaling pathway, effectively blocks vascular endothelial cell proliferation and angiogenesis, making it a key therapeutic agent for the treatment of complex vascular diseases.[7]

Unlike previous studies that primarily focused on the efficacy of topical sirolimus monotherapy, the uniqueness of this study lies in the fact that all patients had undergone an initial course of oral propranolol treatment. Propranolol, by inhibiting angiogenic factors and reducing blood flow supply to the lesion, effectively controls the rapid expansion of the tumor.[8] However, in some patients, the efficacy of oral propranolol gradually stabilizes or stagnates over time, particularly in complex lesions. This study demonstrates that introducing topical sirolimus cream after the discontinuation of propranolol at this plateau stage can significantly enhance therapeutic efficacy. The sequential use of propranolol followed by topical sirolimus appears to provide additive clinical benefits; propranolol controls early tumor growth and vascular activity, while subsequent topical sirolimus contributes further to lesion reduction, particularly in deep-seated or refractory cases.[9]

Topical sirolimus cream has demonstrated significant advantages in the treatment of KHE, as its localized action effectively prevents systemic side effects that may be associated with systemic sirolimus, such as immunosuppression and liver function abnormalities.[10] In this study, none of the patients experienced systemic toxicity after receiving topical treatment, and only a few patients reported mild localized irritation, such as erythema and pruritus, which completely resolved after dose adjustment. This further confirms the favorable safety profile of topical sirolimus in pediatric patients.

However, the limitations of topical sirolimus must still be considered. Its efficacy may be restricted by drug permeability, particularly in cases involving thicker skin or deep-seated lesions. Future research may explore the optimization of drug formulations, such as nanocarrier systems or transdermal enhancers, to improve drug penetration and enhance therapeutic efficacy in complex lesions.[11]

Previous studies have shown that topical sirolimus monotherapy is highly effective in treating superficial lesions but has limited efficacy for deep-seated lesions.[12] In contrast, this study implemented a sequential treatment strategy in which topical sirolimus was introduced following propranolol discontinuation, demonstrating better overall efficacy. Particularly in large or highly vascularized lesions, the sequential treatment approach was associated with improved outcomes while avoiding the potential toxicity of systemic combination therapy. This strategy also appeared to improve treatment adherence.

Although this study highlights the notable advantages of sequential therapy, its small sample size and limited follow-up duration necessitate further research to assess its long-term efficacy and recurrence risk. Future studies should include multicenter randomized controlled trials to further validate the additive effects of propranolol and topical sirolimus. Additionally, optimizing treatment regimens based on different lesion types and individual patient characteristics, as well as exploring more effective drug combinations, will provide crucial support for the personalized treatment of KHE.

Conclusion

In summary, this study demonstrated the significant efficacy of topical sirolimus cream as a follow-up treatment strategy when the therapeutic response to oral propranolol reaches a plateau. By implementing a sequential therapy approach, topical sirolimus was introduced after discontinuation of propranolol, further promoting lesion regression. This approach offers a novel, safe, and effective treatment option for patients with KHE.

Abbreviations

KHE, Kaposiform hemangioendothelioma; KMP, Kasabach-Merritt phenomenon; VAS, Visual Analog Scale.

Data Sharing Statement

All data are available from the corresponding author by request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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