Dermatol Ther (Heidelb) (2023) 13:29–49
https://doi.org/10.1007/s13555-022-00848-1

REVIEW

The Role of Systemic and Topical Beta-Blockers in Dermatology: A Systematic Review

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Received: July 28, 2022 / Accepted: October 31, 2022 / Published online: November 22, 2022

ABSTRACT

Introduction: Beta-blockers are proven to be safe and cost-effective agents in treating multiple dermatological conditions, which is why they are considered as an interesting and good alternative therapeutic agent by dermatologists. To our knowledge, there has been no comprehensive systematic review to date summarizing the role of both systemic and topical beta-blockers in dermatology.

Methods: In this systematic review, we aim to review recent and relevant published literature in order to provide a comprehensive evidence-based summary to inform dermatologists.

Results: An electronic-based literature search was carried out during October–December 2021 in the databases PubMed (MEDLINE), SCOPUS (EMBASE), and Cochrane Library. Furthermore, bibliographic sources were also reviewed for the selected articles. We followed The Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 (PRISMA) guidelines. We reviewed published literature about the role of beta-blockers in dermatology for the time period (January 2016 to December 2021).

Conclusions: A total of 126 publications were retrieved from different databases, of which 59 studies were finally included in our review after excluding non-eligible literature in accordance with our inclusion and exclusion criteria. The included articles consisted of meta-analyses, systematic reviews, clinical trials, retrospective and prospective cohort studies, case–control studies, case series, and case reports. In general, data in reviewed literature showed that both systemic and topical beta-blockers were reliable and safe therapeutic options in treating different dermatoses. Their effect has been studied as a mono-therapy, also as an adjuvant therapy combined with other current disease-specific therapeutic modalities such as lasers, radiation, chemotherapy, corticosteroids, or other beta-blockers options. Local and systemic adverse effects were mainly minor and non-significant.

Keywords: Beta-blockers; Adrenergic beta-antagonists; Dermatology; Dermatological diseases; Skin disorders; Wound healing; Infantile hemangioma; Acne; Rosacea; Skin ulcers; Melanoma; Eczema

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Key Summary Points

Beta-blockers are safe and cost-effective agents in treating multiple dermatological conditions.

They are considered as good alternative therapeutic agents by dermatologists, they can be used as a mono-therapy, or as an adjuvant therapy combined with other current disease-specific therapeutic modalities.

Their role has been reviewed for several dermatological disorders in 2017 and 2018, furthermore, new dermatological conditions have been reviewed in this article such as acne vulgaris, atopic dermatitis, telangiectasia, ulcers, and keloids.

Although studies showed promising outcomes, further research is needed to provide more information in order to provide sufficient evidence.

INTRODUCTION

The use of beta-blockers in treating cutaneous diseases has been expanding among dermatologists worldwide over the past decade. Since the first coincidental discovery of the therapeutic effect of propranolol on infantile hemangioma by Leaute-Labreze et al. [1], research has been carried out in order to investigate their efficacy and safety in treating other skin diseases. In general, beta-blockers are proven to be safe and cost-effective agents, which is why they are considered a good alternative by dermatologists.

Beta-blockers, also known as beta-adrenergic receptors (ß-AR) antagonists, are a class of medications that are primarily used to treat cardiovascular diseases. There are three types of ß-ARs: ß1-AR, ß2-AR, and ß3-AR, which are located primarily in the heart and different tissue organs. ß2-AR is found to be highly expressed in major skin cell types; keratenocytes[2], fibroblasts [3], melanocytes [4] and secretory coil of apocrine glands [5]. Therefore, ß2-ARs antagonists are the most commonly used in dermatology. They are available for administration orally, intravenously, and topically.

To our knowledge, there has been no comprehensive systematic review to date summarizing the role of both systemic and topical beta-blockers in dermatology. Systematic reviews are robust evidence that consolidate extensive overview and deliver more reliable and clear answers to inform physicians. They are essential for clinical practice in order to guide clinicians and ensure the optimal care for patients. Moreover, it will help in identifying research gaps in this topic for further research. Thus, we are aiming to review recent and relevant published literature in order to provide a holistic evidence-based summary about the role of beta-blockers in dermatology.

METHODS/LITERATURE SEARCH

For this systematic review, an electronic-based literature search was carried out during October to December 2021 in the databases PubMed (MEDLINE), SCOPUS (EMBASE), and Cochrane Library. Furthermore, bibliographic sources were also reviewed for the selected articles. The Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 (PRISMA) guidelines were followed [6]. All published literature about the role of beta-blockers in dermatology for the period between January 2016 and December 2021 were searched. MeSH terms/keywords were used to build for our search, such as beta-blockers, adrenergic beta-antagonists, dermatological diseases, or skin disorders. We were primarily seeking literature about the use of beta-blockers in dermatology. For the search techniques and medical subject headings, different combinations of keywords were used. A detailed search strategy can be found in the supplements. This review included all research articles that were published between the years 2016 and 2021 on the role of beta-

blockers in treating various dermatoses. Non-human subject research and non-English studies were omitted.

During the preliminary literature search, screening and eligibility assessment were carried out independently by two authors. The publications were first screened based on their titles, then the abstracts, all irrelevant articles were excluded in the secondary screening, and relevant articles were chosen for full-text screening. The full-text screened publications were also eliminated when there was a lack of information relevant to our research goal. From the selected articles, author names, year of publication, sample size, research design, level of evidence, dermatoses, interventions and outcomes were retrieved.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Eligible Studies

A total of 126 publications were retrieved from different databases, of which 59 articles were included in our review after excluding non-eligible papers, in accordance with our inclusion and exclusion criteria (Fig. 1). The included articles comprised 16 meta-analyses and systematic reviews, 18 clinical trials, 20 observational cohort studies and case–control studies, five case series and case reports. The relevant findings of the included studies are summarized in Tables 1, 2, 3, 4, 5, and 6.

Mechanism of Action

The exact mechanism of action of beta-blockers in dermatological conditions is likely multifactorial and unclear. Researchers have proposed several theories to interpret their therapeutic effects in various dermatoses [7]. In general, they may inhibit angiogenesis in dermatoses of vascular origin, such as rosacea [8], inhibit β-adrenergic receptors in melanocytes, and slow tumor growth in dermatoses of non-vascular origin, such as melanoma [9], and may also promote wound healing [10].

Mode of Administration

In dermatology, beta-blockers are either orally or topically administered, depending on the medication type, severity of the condition, and disease presentation. Propranolol, atenolol, bisoprolol, nadolol, and carvedilol are the most common systemically administered beta-blockers in dermatology (Tables 1, 2, 3). Similarly, timolol, propranolol, betaxolol, and carteolol are the most common agents topically applied as creams, solutions, gels, and ointments (Tables 4, 5, 6).

Dermatoses and the role of beta-blockers

Previously reviewed dermatoses:

Infantile hemangioma/PHACE/LUMBAR syndrome

Systemic beta-blockers

Multiple studies have demonstrated the efficacy and safety of oral propranolol for infantile hemangioma (IH) in term and preterm infants, including superficial, deep, and even syndromic cases, including PHACE [11]. A study by Bayrart et al. [12] concluded that atenolol is at least as effective as propranolol and exhibits a lower risk of bronchospasm. In addition, a study by Gumina et al. [13] used atenolol as a substitute for propranolol for the management of sleep disturbances in the treatment of IH, which resulted in improvement or resolution of sleep issues in most patients. However, propranolol did not substantially impair the sleep quality and pattern [14]. No increased risk of adverse effects was observed in preterm versus term patients treated with oral propranolol [15].

Topical beta-blockers

Beta-blockers can be used as monotherapy or in combination with other systemic therapies for mixed IH [16]. Topical timolol 0.5% gel was favored over topical timolol maleate 0.1% and topical propranolol [17]. No differences were observed in the reduction of SIH size from either oral propranolol or topical timolol maleate, with the advantage of topical

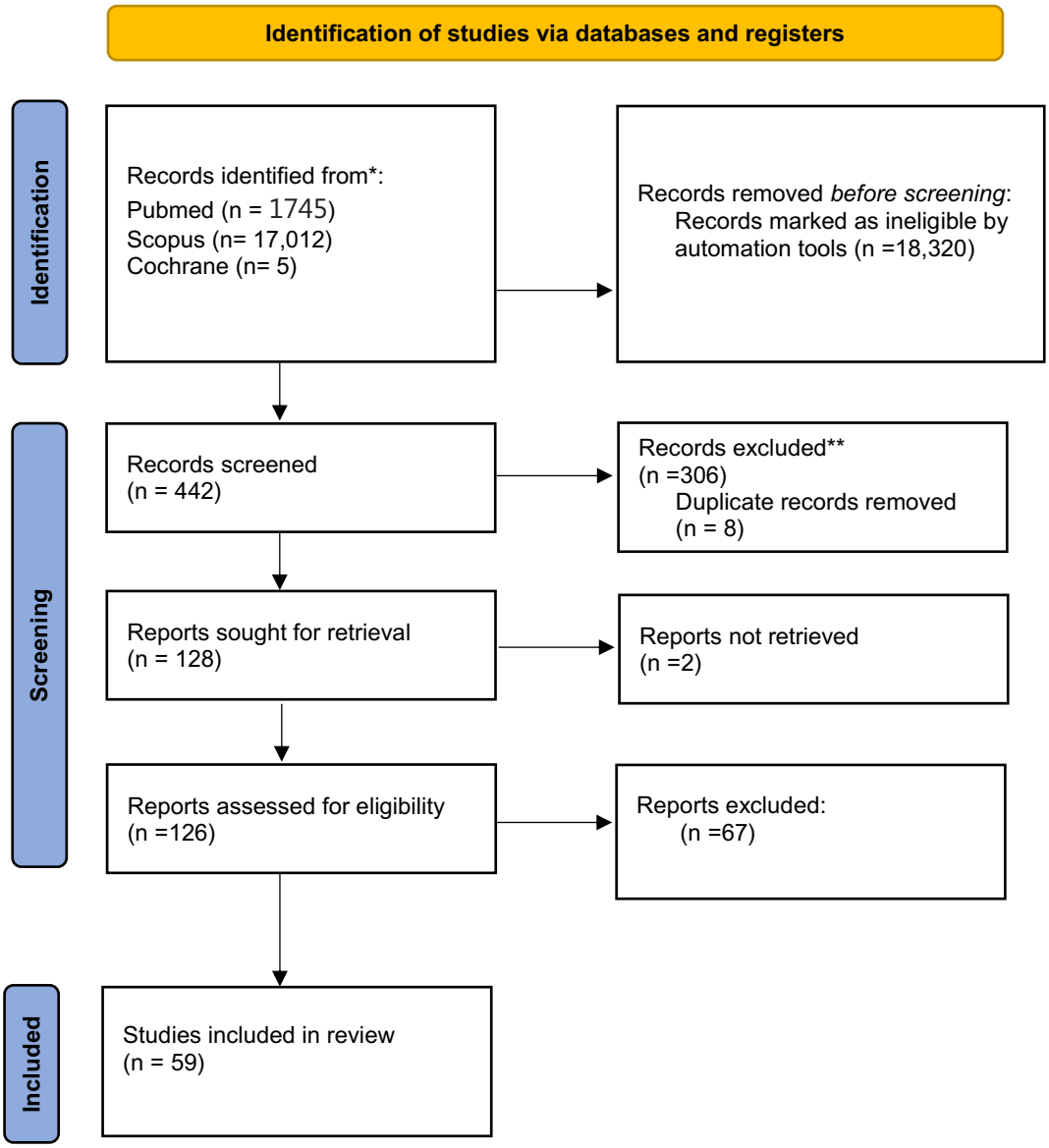

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews

administration being minimal absorption and systemic adverse effects [18]. However, topical administration appears to have a slower onset of action (12–16 weeks) [19]. These results may replace oral propranolol as a first-line therapy for SIH, and they are of additive value in treating MIH when combined with other interventions [16]. However, a study by [17] Randall A. et al. warned about their use in lesions located on mucosal surfaces and in the periocular region due to unpredictable systemic absorption.

Pyogenic granuloma

Topical beta-blockers

Propranolol gel (4%, twice daily) was evaluated; most patients had complete or almost complete resolution, and only a minority experienced local irritation [20]. In RCTs comparing topical timolol, propranolol, and placebo, topical beta-blockers twice daily achieved complete resolution in most of the patients

Table 1 Systemic beta-blockers in dermatological therapy (systematic reviews and meta-analysis)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Oral propranolol/1–3 mg/kg/day/BID—TID	Léaute-Labrèze et al. 2016 [51]/Systematic review including 83 articles with 3766 propranolol-treated patients	1a	NM	Well tolerated	Sleep disturbances, peripheral coldness, and agitation
	Oral propranolol/1 then 2–3 mg/kg/day for 6 m	Léauté-Labrèze et al. 2017 [52]/Systematic review including RCT, a large cohort study, and a meta-analysis of 1264 cases	1a	NM	96–98% complete regression 60% nearly complete regression	Reversible and mostly benign
	Oral propranolol/1–4 mg/kg/day	Novoa et al. 2019 [18]/Systematic review including 28 RCTs (1728 participants) assessed 12 interventions	1a	–	Increased IH clearance	No increase in harm
	Oral propranolol/3 mg/kg/day	Mellerio [53]/Review including 5 RCTs with of 379 children	1a-	–	Increased IH clearance	No serious AEs
	Oral propranolol/2–3 mg/kg/day	Al-Haddad et al. 2019 [54]/Review including 7 RCTs	1a	Periocular	Hemangioma shrinkage	Mild GI symptoms, sleep disturbances, cool or sweaty extremities
	Oral propranolol/2-3 mg/kg/day	Oberlin et al. 2017 [55]/Review	2a	–	Propranolol is effective and safe	Not reported

Table 1 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
	Oral propranolol with lasers	Chen et al. 2020 [19]/Systematic review and meta-analysis/14 literature including 2658 patients	1a	Head, face, trunk, limps and premium	Combined therapy was significantly more effective than monotherapy	No statistically significant differences of AEs
Rosacea	Carvedilol 3.125–6.25 mg BID or TID/propranolol 10–40 BID or TID/nadolol 40 mg BID or TID	Logger et al. 2020 [24]/Systematic review/9 studies including 64 patients	1a	Face	Less erythema and flushing	Bradycardia and hypotension were the most commonly described AEs
Melanoma	Beta-adrenergic blockers	Williams et al. 2020 [9]/Review	1b	–	Beta-blocker does not seem to be associated with the development of melanoma	Not reported

[21]. No substantial difference was observed in the clinical responses of the beta-blockers groups [21]. Topical timolol (0.5% gel, twice daily) was evaluated for EGFR-induced pyogenic granuloma-like lesions and paronychia. Complete and partial response was observed in 52% of the lesions; partial response was achieved in 36% [22].

Rosacea and acne

Topical beta-blockers

Al Mokadem et al. [23] conducted a multicentric interventional study that included an equal number of acne and rosacea patients (58 patients for each disease). Application of 0.5% topical timolol maleate each night for 8 weeks markedly reduced the number of comedones, papules, total lesion count, pustules, and acne severity. However, the improvement in rosacea was not statistically significant.

In addition to carvedilol and nadolol, propranolol has also been studied for rosacea and acne. Jade Logger et al. [24] reviewed their role in nine articles (one RCT, one cohort study, one case–control study, three case reports, and three case series). Propranolol and carvedilol were the most effective in reducing erythema and flushing with a rapid onset of symptom control; however, nadolol did not show similar results.

Melanoma

Systemic beta-blockers

De Giorgi et al. [25] studied the effect of beta-blockers exposure on reducing the risk of progression of thick malignant melanoma in a prospective study during 2011–2013. A total of

53 patients, with histologically confirmed stage IB to IIIA cutaneous melanoma and no evidence of metastasis, participated in the study and were divided into 19 cases and 34 controls. The cohort patients were instructed to take oral propranolol (80 mg daily) as an off-label adjuvant treatment. After a median follow-up of 3 years, they concluded that propranolol protected patients from disease recurrence and death.

After a median follow-up time of 8 years and a median duration of beta-blockers use of 7.6 years, De Giorgi et al. [26] carried out another prospective study in 2020 on previously included patients with malignant melanoma stage II–IIIA (T2, N0 or N1, M0). They found that 45% of the patients in the untreated group and 30% of the patients in the treated group had disease progression. Thirty-two patients (35%) in the untreated group and five patients (17%) in the treated group died from melanoma. The initial result of the difference in mortality was confirmed after a longer follow-up period.

Dimitrios Katsarelias et al. [27] conducted a nationwide Swedish population-based retrospective register study on 12,738 patients, of which 3702 were exposed to beta-blockers and 9036 were non-exposed patients. In their study, they could not confirm the finding that the use of beta-blockers had a positive impact on survival in patients with melanoma.

Currently reviewed dermatoses:

Post-acne erythema

Topical beta-blockers

A study by Afra T.P. et al. [28] demonstrated the therapeutic effect of topical timolol maleate 0.5% ophthalmic solution in a case of remarkable post-inflammatory erythema and atrophic scars. They observed a significant improvement in post-inflammatory erythema; only shallow rolling scars were left with no pigmentation. No local or systemic adverse effects were noted.

Acne scars

Topical beta-blockers

A double-blind clinical trial of 25 participants with atrophic acne scars, who underwent ablative fractional carbon dioxide laser therapy, demonstrated the effect of the application of topical 0.5% timolol after laser therapy, where it restored the skin barrier compared with placebo [29]. No local or systemic adverse effects were reported [29].

Keloids

Systemic beta-blockers

In a single-institution case–control study, the effect of the administration of beta-blockers (carvedilol, bisoprolol, and atenolol) was observed in treating scars and keloids after pacemaker implantation in 45, 12, and 33 patients, respectively [30]. They found that patients with keloids or hypertrophic scars, after cardiac device implantation, tended to be less likely to take beta-blockers than control patients with normal scars.

Ulcers and wounds

Topical beta-blockers

In a clinical trial, Abdelmaksoud et al. [31] studied three patients with chronic leprosy ulcers after completing the WHO-recommended regimen (1% topical propranolol in liposomal gel for 3 months). Two of the three patients showed complete healing of the ulcers at the 6-month follow-up. In the third patient, the ulcer showed only modest signs of healing. Sensory function, particularly in terms of pain, was restored in all patients.

Ganary Dabiri et al. [32] found that the application of topical timolol on wounds and scars resulted in cosmetically favorable effects compared to controls.

Vestita et al. [33] studied one patient with a deep chronic ulcerating lesion of the right sole who was treated with topical propranolol for 3 weeks. At the end of the treatment period, the ulcer had dramatically improved, and after another week, the lesion had completely healed; then, at the follow-up 1 year later, no recurrence was seen.

They also reported a retrospective study [34] that included 82 patients affected by non-healing loss of substance associated with diverse etiologies (venous, diabetic, post-surgery, post-radiation, pressure, mistreated burns). All patients were administered topical timolol for 6 weeks and received an appropriate standard of care. A statistically significant improvement in the percentage of area reduction (up to 98.75%) and mean size was noted in all groups except for diabetic and pressure ulcers.

Table 2 Systemic beta-blockers in dermatological therapy (interventional studies)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Oral propranolol/2 mg/kg/day/TID	Kim et al. 2017 [56]/RCT/34 patients	1b	Scalp, chest, face, abdomen, back, and extremities	Propranolol efficacy was not inferior to steroids	No difference in safety outcomes
	Oral propranolol/2 mg/kg/day	Hu et al. 2016 [57]/RCT/76 patients	1b	Faciocervical, trunk, and extremities	Increased IH clearance	Safe for IH in pediatric population
	Oral propranolol/2 mg/kg/day	Zaher et al. 2016 [58]/RCT/30 patients	1a	–	Propranolol superior to captopril	Not observed
	Oral propranolol/3 mg/kg/day/BID	Baselga et al. 2018 [59]/Clinical trial/45 patients	1b	Periorbital, nasal, labial, laryngotracheal, limb joints, glabella, philtrum, chin, and cheek	Treatment was effective in most patients with high-risk IH	Bradycardia
	Oral propranolol/2 mg/kg/day/TID	Kagami et al. 2018 [60]/Clinical trial/32 patients	1b	Face, chest, neck, back, scrotum, and extremities	Propranolol was effective and safe	Not observed
	Oral propranolol/3 mg/kg/day	Kaneko T et al. 2017 [61]/Clinical trial/32 patients	1b	Face and other body parts	Propranolol was effective and safe	No serious AEs
	Propranolol 2 mg/kg/day and oral atenolol 1 mg/kg/day	Ashraf R et al. 2019 [62]/RCT/40 patients	1b	–	Propranolol and atenolol were comparable in efficacy	No serious AEs

Table 2 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
	Propranolol 1–4 mg/kg/day and oral atenolol 1 mg/kg/day	Bayart et al. 2017 [12]/Clinical trial/50 patients	1b	Diaper, eye lid, nose, face, extremity, scalp, and trunk	Atenolol is at least as effective as propranolol	Atenolol poses less risk of bronchospasm

Systemic beta-blockers

Rai et al. conducted the first randomized control trial to study the effect of topical timolol on wound healing in 20 patients with chronic leg venous ulcers [35]. They demonstrated a substantial reduction in the size of the ulcer in patients in the timolol group (86.80%) compared to that in patients in the saline group (43.82%) after 4 weeks of treatment. No side effects were observed, and the treatment was well tolerated [35].

Eczema

Topical beta-blockers

Pawar et al. [36, 37] conducted two clinical trials that included one patient with eczema in each to study the effect of topical timolol on erosions and fissures on palms of hands and heels of feet. Healing of erosions and fissures was observed in both studies.

Topical glucocorticoid-induced skin telangiectasia

Topical beta-blockers

Li et al. investigated the potential effect of topical timolol maleate (0.5%) eye drops (TMEDs) on topical glucocorticoid-induced skin telangiectasia [38]. A total of 30 female patients with facial skin telangiectasia were included, wherein one cheek of each patient was assigned to the treatment group and the other to the control group. For the treatment group, topical twice-daily application of TMEDs was combined with 0.1% tacrolimus ointment once or twice daily for 8 weeks. Cheeks in the control group were administered 0.1% tacrolimus ointment alone. After 4 weeks, marked improvements in erythema and telangiectasia were observed in the treatment group. In addition, marked subsidence of expanded capillaries was observed after 8 weeks of treatment, in contrast to the control group, wherein telangiectasia remained clearly visible. No adverse effects were observed.

Kaposi sarcoma

Topical beta-blockers

A study by Abdelmaksoud et al. [39] reported the efficacy of topical timolol gel in a case series of four patients with Kaposi sarcoma (KS) on antiretroviral therapy, three with the classical type and one with HIV; all patients showed significant improvement.

DISCUSSION

This review emphasizes that beta-blockers have been proven to be safe and well tolerated in treating several dermatological disorders, they are cost-effective, and easily available alternative/adjuvant therapies in dermatology.

To date, propranolol is the only FDA-approved beta-blocker for therapeutic use in IH [19, 40], other beta-blockers are being used off-label to treat various skin conditions. They were used as a monotherapy or in combination with other treatment modalities such as lasers, radiation, chemotherapy, corticosteroids, or others.

Among all, IH was mostly investigated. They studied the therapeutic effect of beta-blockers in different types of IH, also, favorable drug options, settings, and regimens. Essentially, beta-blockers were safe and well tolerated in the treatment of IH in both systemic and topical

Table 3 Systemic beta-blockers in dermatological therapy (observational studies, case series/report)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Oral propranolol/2 mg/kg/day	Li et al. 2019 [15]/Retrospective study/235 patients	2b	Head, neck, trunk, and extremities	Propranolol was not associated with a higher incidence of AE	Propranolol was not associated with a higher incidence of AE
	Oral propranolol/2 -3 mg/kg/day	Lahrichi et al. 2018 [63]/Prospective study/121 patients	2b	Face and neck	Treatment proved to be safe and effective	Not reported
	Oral propranolol/2 mg/kg/day	Tan et al. 2021 [64]/Retrospective review/88 patients	2b	Head, neck, trunk, groin, and upper limps	Treatment proved to be safe and effective	Low incidence of AEs
	Oral propranolol/2 mg/kg/day	Frost et al. 2021 [14]/Prospective pilot study/55 patients	2b	–	No significant difference was found in sleep quality	Not reported
	Oral propranolol/2 mg/kg/day/TID	Turhan et al. 2016 [65]/Retrospective study/34 patients	2b	Face, head, neck, trunk, extremities	Propranolol was a well-tolerated, efficacious, and safe drug	Not observed
	Oral propranolol	Tognetti et al. 2020 [66]/Prospective study/94 patients	2b	Head, neck, trunk, extremities, perineal	HRVD allows a real time monitoring of vascular changes in IH treated with oral propranolol	Not reported
	Oral propranolol/2-3 mg/kg/day/BID or TID	Schwartz et al. 2017 [67]/Literature review	2a	Subglottic	Propranolol was effective	Not reported

Table 3 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
	Propranolol combined with topical timolol	Mannschreck et al. 2019 [68]/Retrospective review/559 patients	2b	–	Minimize potential AE of systemic treatment	Not reported
	Oral propranolol and topical timolol/2 mg/kg/day/BID timolol maleate 0.5% gel/TID	Ge et al. 2016 [69]/Retrospective study/89 patients	2b	Head and face	Clinical response in 100% of the patients	Few minor AEs were noted: cold extremities agitation during the night and diarrhea
	Atenolol 0.3–1 mg/kg/day/NM	Gumina et al. 2019 [13]/Case series/4 patients	4	Face and neck	Atenolol does not cause sleep disturbance	Sleep disturbance with propranolol
LUMBAR syndrome	Oral propranolol/2 mg/kg/day	Yu et al. 2017 [70]/Case report/1 patient	4	Lower extremity, perineum, and gluteal region	Increase IH clearance	No reported AEs
PHACE syndrome	Oral propranolol/0.3 mg/kg/day or more	Olsen et al. 2019 [11]/Retrospective cohort study/76 patients	2b	–	No serious AEs during treatment with propranolol	No serious AEs
Rosacea	Carvedilol 12.5 mg daily	Seo et al. 2020 [71]/Retrospective review/24 patients	2b	Face	Less erythema and flushing	Mild dizziness and GI discomfort

Table 3 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Melanoma	β-adrenergic blockers	Katsarelias et al. 2020 [27]/ Retrospective registry study/ 12,738 patients	2b	–	No conclusion on survival in melanoma patients	Not reported
	β-adrenergic blockers	De Giorgi et al. 2017 [72]/ Prospective review/121 patients	2b	–	Beta-blockers reduced the risk of recurrence and mortality	Not reported
	Oral propranolol/ 80 mg OD	De Giorgi et al. 2018 [25]/ Prospective cohort study/ 53 patients	2b	–	Beta-blockers protect patients from melanoma recurrence	No AEs in the PROP group
Keloid	Carvedilol, bisoprolol and atenolol	Enoshiri et al. 2017 [30]/ Case–control/ 60 patients	3b	–	Effective for preventing and treating keloids	Not reported

*Oxford Centre for Evidence-based Medicine: Levels of Evidence (March 2009) [73]

formulations at all levels of evidence. However, a case of severe transient hypertriglyceridemia was recently reported to be associated with administering systemic propranolol for treating ulcerated IH in a 1-month-old infant. Further research is needed to explore this association [41]. Topical beta-blockers were particularly beneficial for treating superficial IH. The role of beta-blockers was investigated as a monotherapy, and adjuvant therapy where combination of beta-blockers with other modalities induced a synergistic effect that improved the outcome and reduced the duration of treatment and adverse effects. Although propranolol is the treatment of choice for both proliferating and ulcerated IH, pulsed dye lasers still play a major role in residual IH [42]. Moreover, treating IH with propranolol was more cost-effective when delivered in outpatient settings [43]. Monitoring of vital signs is not necessary in normal conditions [44], and routine cardiac screening using electrocardiogram and echocardiogram prior to outpatient visits is not definitely indicated [45]. There was no definite conclusion for the duration of using propranolol, as well as when to stop and how. However, an appropriate time to retain efficacy and avoid adverse effects is suggested. Ultrasound is helpful in assessing treatment efficacy upon termination by measuring IH thickness and vascularity [46]. Patients with IH who received oral propranolol should be followed up to at least 6 months [47].

Table 4 Topical beta-blockers in dermatological therapy (systematic reviews and meta-analysis)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Topical timolol maleate 0.5%/BID	Novoa et al. 2019 [18]/Cochrane systematic review/1728 patients	1a	–	Decreased redness	No increase in harm
	Topical timolol maleate 0.5%/BID	Mellerio et al. 2019 [53]/Abridged review	3a	–	Decreased redness	Not reported
	Topical timolol	Al-Haddad et al. 2019 [54]/Review/–	1a	Periorbital	Improvement, esp. superficial IH	Mild GI symptoms, sleep disturbances, cool, or sweaty extremities
	Topical timolol/BID	Khan et al. 2017 [74]/Systematic review and meta-analysis/31 studies of 691 patients	1a	–	Improvement of small IH, 91% resolution rate	No significant AE noted
	Topical timolol 0.5% gel forming solution	Randall Bly 2017 [17]/Review/-	2a	Head and neck	Timolol 0.5% gel forming solution is preferred over other topical beta-blockers	Safe treatment
	Topical timolol	Wang et al. 2021 [16]/Meta-analysis including 11 RCTs with 1235 patients	1a	Multiple areas	Topical beta-blockers are as effective as oral propranolol	Less AEs than oral propranolol

Topical beta-blockers have been proven to be efficacious and safe in treating PG as well, mostly for small, superficial infantile PG and PG-like lesions induced by EGFR-I [22]. They can postpone or obviate surgical treatment, especially in children, for whom they are the first-line treatment, also, in large lesions by reducing its size. The only limitation of beta-blockers here is their inability to perform histological examinations [48]. Although the adverse effects and systemic absorption appeared to be negligible in all included studies,

Table 5 Topical beta-blockers in dermatological therapy (interventional studies)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Topical timolol and PDL/(5 ml: 25 mg) TID (for 20 min each)	Chen et al. 2021 [75]/RCT/20 patients	1b	Vulva or scrotum, perianal region, buttocks, lip, and trunk	Effective	No significant AEs
Pyogenic granuloma	Propranolol 1% cream. Timolol 0.5% cream/ BID	El-Taweel et al. 2021 [21]/ Interventional study/30 patients	2b	Hands, neck, and limps	Complete resolution with no recurrence	No local or systemic AE noted
Acne (scars, erythema)	Timolol maleate 0.5%/OD	Al Mokadem et al. 2020 [23]/ Clinical trial/58 patients	1b	Face	Decrease severity of acne	Mild and tolerable
	Timolol maleate 0.5%/BID	Kimwattananukul et al. 2021 [29]/ Clinical trial/25 patients	1b	Face	Enhanced skin-barrier function and wound healing	Not observed
Wounds	Topical timolol	Dabiri et al. 2017 [32]/RCT/9 patients			Timolol resulted in more cosmetically favorable scars	Not observed
Chronic leprosy ulcers	Topical 1% propranolol/ BID	Abdelmaksoud et al. 2018 [31]/ Clinical trial/3 patients	1b	Sole of foot	Improvement of leprosy ulcers	No local or systemic AEs
Chronic recalcitrant wound	Galenic preparation of 1% propranolol-hydrochloride/ TID	Vestita et al. 2016 [33]/Clinical trial/1 patient	1b	Sole of foot	Complete healing of ulcer	No local or systemic AEs

Table 5 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Fissures and erosions of hand eczema	Timolol 0.5% ophthalmic solution, 2–3 drops OD	Manoj Pawar 2021 [36]/Clinical trial/1 patient	1b	Palms of hands	Healing of erosions and fissures	Not observed
Deep fissures of heels	Timolol 0.5% ophthalmic solution, 2–3 drops OD	Manoj Pawar 2021 [37]/Clinical trial/1 patient	1b	Heels of feet	Healing of fissures with no recurrence	Not observed
Topical glucocorticoid-induced skin telangiectasia	Timolol maleate 0.5%/eye drops BID	Li et al. 2018 [38]/RCT/30 patients	1b	Face	Improvement in erythema and telangiectasia	No AEs

further research is needed to identify the maximal dosage and duration.

Their role in rosacea was limited to reducing the non-inflammatory lesions of acne and the symptoms of erythematotelangiectatic rosacea. It showed a modest therapeutic effect in papulopustular rosacea [23]. Similarly, topical timolol was only beneficial in alleviating the symptoms of telangiectasia in facial corticosteroid addiction dermatitis symptoms; other symptoms were not investigated [38]. They can also be considered as a great adjuvant therapy in melanoma, as they improved morbidity and mortality.

In addition to previously reviewed dermatoses in 2017 and 2018 [49, 50], our systematic review included recent studies about the role of beta-blockers in different dermatological diseases. Topical timolol resulted in favorable outcomes in post acne erythema and scars [23, 28, 29]. It resulted in decreased acne severity, less erythema, and pigmentation. It also showed an improvement in erythema and telangiectasia in topical glucocorticoid-induced skin telangiectasia [38]. In keloids [30], they yielded good results in treating and preventing as well. Most recently, topical timolol showed an interesting and promising effect in eczema; its effect was reported in treating non-healing erosions and fissures of palms of the hand as well as heels of feet [36, 37]. Although there are new studies on the role of beta-blockers in dermatology, however, the evidence is not sufficient yet to be conclusive. Further studies are needed to provide vital information including the optimal dosing, type, and duration of treatments, efficacy, as well as adverse events.

In this systematic review, the heterogeneity of the evidence created a challenge in shaping a concise and comprehensive summary. Each type of evidence posed distinct sources of bias and limitations. Common limitations of clinical trials include small sample size that affected the robustness of their findings, and specific population characteristics such as skin phototype, which restricted generalizability. A short treatment period was also a drawback in some trials because some biophysical parameters had not returned to baseline by the end of the study. Although no abnormal symptoms were reported, vital signs were not monitored, which would have helped to precisely detect possible side effects such as bradycardia or hypotension. Stronger evidence than case series/studies was required to determine the best therapeutic types, vehicles, and regimens for beta-blockers.

Table 6 Topical beta-blockers in dermatological therapy (observational studies, case series/report)

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
Infantile hemangioma	Propranolol 1% cream, timolol 0.5% cream/QID	Ying et al. 2017[76]/Prospective study/21 patients	2b	Extremities, trunk, hand	Significant clinical improvements in both treatments	No permanent AEs
	Carteolol 2% drops/BID	Gan et al. 2017 [77]/Prospective study/349 children	2b	Head, neck, trunk, and hand or leg	Effective with proliferative superficial IHs	No AEs noted
	Topical propranolol 4%/BID	Mashiah et al. 2017 [78]/Retrospective study/63 patients	2b	Head, neck, trunk, extremities, and genital area	Good to partial response	Minor local AEs
	Oral Propranolol and topical Timolol/NM	Mannschreck et al. 2019 [68]/Retrospective study/559 patients	1b	–	Minimized potential AE of systemic treatment	Not reported
Pyogenic granuloma	- Topical timolol 0.5% gel/BID - Propanolol 1% cream/OD - Betaxolol 0.25% eye drops/OD	Sollena et al. 2019 [22]/Case series/9 patients	4	Feet and hands	Complete resolution to partial improvement	No systemic AEs reported
	Propranolol 4% gel/BID	Mashiah et al. 2019 [20]/Uncontrolled retrospective study/18 patients	2b	Cheek, neck, arm, labia, chest, forehead, and scalp	Complete to almost complete resolution	local AEs in 1 patient

Table 6 continued

Dermatoses	Treatment/dose/frequency	Study/study design/sample size	Level of evidence*	Affected area	Outcomes	
					Efficacy	Adverse events (AEs)
	Propranolol ointment 1%/BID	Neri et al. 2018 [79]/Prospective study/22 patients	2b	Chest, back, face, upper extremities, and scalp	59% completely regressed, 18.2% remained stable, and 22.7% did not respond	No AEs were observed
Acne (scars, erythema)	Timolol maleate 0.5%/One drop	Afra et al. 2021[28]/Case report/1 patient	4	Face	Less erythema Less pigmentation	Not observed
Kaposi sarcoma	0.1% timolol gel/BID	Abdelmaksoud et al. 2017 [39]/Case series/4 patients	4	Leg, foot, arm	Complete resolution of lesions, edema, and pain	No reported adverse events 4 to 5 weeks later

*Oxford Centre for Evidence-based Medicine: levels of evidence (March 2009) [73]

Also, this study was restricted to a certain time scope, in which some dermatological diseases such as angiofibromas, angiolymphoid hyperplasia with eosinophilia, and angiosarcoma could not be addressed. However, they were explicitly reviewed by Chen et al. [50], in which they concluded the effectiveness of beta-blockers in treating dermatoses of vascular origin and promoting wound healing.

CONCLUSIONS

Beta-blockers are proven to be safe and cost-effective agents in treating multiple dermatological conditions. Thus, dermatologists should consider them as good alternative/adjuvant therapies in treating several skin conditions.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study. The publication of this article was funded by the authors.

Author Contributions. All named authors have contributed to this manuscript. They contributed in concept and design, building search strategy, searching literature, retrieving information, quality assessment, collecting results, drafting the manuscript, and writing the paper.

Disclosures. Alya M. Alhazmi, Mohammad A. Basendwh, Abdullah Ayman Aman, Mazen Dajam, Turki S. Aljuhani have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with

human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Léauté-Labrèze C, De La Roque ED, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649–51.

2. Steinkraus V, Steinfath M, Körner C, Mensing H. Binding of beta-adrenergic receptors in human skin. J Invest Dermatol. 1992;98(4):475–80.

3. Pullar CE, Isseroff RR. ß2-adrenergic receptor activation delays dermal fibroblast-mediated contraction of collagen gels via a cAMP-dependent mechanism. Wound Repair Regen. 2005;13(4):405–11.

4. Autocrine Catecholamine Biosynthesis and the β2-Adrenoceptor Signal Promote Pigmentation in Human Epidermal Melanocytes - ScienceDirect [Internet]. [cited 2022 Jan 14]. Available from: https://www.sciencedirect.com/science/article/pii/S0022202X15309167

5. Innervation and receptor profiles of the human apocrine (epitrichial) sweat gland: routes for intervention in bromhidrosis - Lindsay - 2008 - British Journal of Dermatology - Wiley Online Library [Internet]. [cited 2022 Jan 14]. Available from: https://onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1111/j.1365-2133.2008.08740.x

6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;29(372): n71.

7. Puspitasari GD, Prawitasari S. Combining topical therapy and bisoprolol on refractory venous ulcer. J Dermatol Venereol Aesthetic. 2020;1(2):84–94.

8. Hajighasemi F, Mirshafiey A. Propranolol effect on proliferation and vascular endothelial growth factor secretion in human immunocompetent cells. J Clin Immunol Immunopathol Res. 2010;2(2):22–7.

9. Williams NM, Vincent LT, Rodriguez GA, Nouri K. Antihypertensives and melanoma: an updated review. Pigment Cell Melanoma Res. 2020;33(6):806–13.

10. β-Adrenergic Receptor Antagonists Accelerate Skin Wound Healing - Journal of Biological Chemistry [Internet]. [cited 2022 Jan 14]. Available from: https://www.jbc.org/article/S0021-9258(18)95250-6/fulltext

11. Olsen GM, Hansen LM, Stefanko NS, Mathes E, Puttgen KB, Tollefson MM, et al. Evaluating the safety of oral propranolol therapy in patients with PHACE syndrome. JAMA Dermatol. 2020;156(2):186–90.

12. Bayart CB, Tamburro JE, Vidimos AT, Wang L, Golden AB. Atenolol versus propranolol for treatment of infantile hemangiomas during the proliferative phase: a retrospective noninferiority study. Pediatr Dermatol. 2017;34(4):413–21.

13. Gumina ME, Yan AC. Atenolol as an alternative to propranolol for the management of sleep disturbances in the treatment of infantile hemangiomas. Pediatr Dermatol. 2019;36(4):556–7.

14. Frost S, Saddi V, Teng A, Mallitt KA, Adams S, Williamson B, et al. Propranolol's effects on the sleep of infants with hemangiomas: a prospective pilot study. Pediatr Dermatol. 2021;38(2):371–7.

15. Li L, Wei L, Xu ZG, Ma L. No Increased risks associated with propranolol treatment for infantile hemangioma in preterm infants were identified at 3 years of age. Am J Clin Dermatol. 2019;20(2):289–93.

16. Wang X, Feng W, Zhao X, Liu Z, Dong L. The efficacy and safety of topical β-blockers in treating infantile hemangiomas: a meta-analysis including 11 randomized controlled trials. Dermatology. 2021;237(3):433–43.

17. Bly RA, Perkins J, Parikh SR. Can topical beta-blockers reduce the size of superficial infantile hemangiomas of the head and neck? Laryngoscope. 2017;127(1):4–5.

18. Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Pardo-Hernandez H, et al. Interventions for infantile haemangiomas of the skin: abridged Cochrane systematic review and GRADE assessments. Br J Dermatol. 2019;180(3):527–33.

19. Chen X, Guo Y, Wang P, Qiu F, Sun Y, Shi Q, et al. Efficacy and safety of adrenergic beta-antagonist combined with lasers in the treatment of infantile hemangiomas: a meta-analysis. Pediatr Surg Int. 2020;36(10):1135–47.

20. Mashiah J, Hadj-Rabia S, Slodownik D, Harel A, Sprecher E, Kutz A. Effectiveness of topical propranolol 4% gel in the treatment of pyogenic granuloma in children. J Dermatol. 2019;46(3):245–8.

21. El-Taweel AEAI, Al-Refaie AAASA, Salem KHA, Salem RM. Topical β-blockers for pyogenic granulomas: a promising option for younger patients. J Cosmet Dermatol. 2021;20(6):1801–6.

22. Sollena P, Mannino M, Tassone F, Calegari MA, D'Argento E, Peris K. Efficacy of topical beta-blockers in the management of EGFR-inhibitor induced paronychia and pyogenic granuloma-like lesions: case series and review of the literature. Drugs Context. 2019;6(8): 212613.

23. Al Mokadem SM, Ibrahim ASM, El Sayed AM. Efficacy of topical timolol 0.5% in the treatment of acne and rosacea: a multicentric study. J Clin Aesthetic Dermatol. 2020;13(3):22–7.

24. Logger JGM, Olydam JI, Driessen RJB. Use of beta-blockers for rosacea-associated facial erythema and flushing: a systematic review and update on proposed mode of action. J Am Acad Dermatol. 2020;83(4):1088–97.

25. De Giorgi V, Grazzini M, Benemei S, Marchionni N, Botteri E, Pennacchioli E, et al. Propranolol for off-label treatment of patients with melanoma. JAMA Oncol. 2018;4(2): e172908.

26. The Role of β-Blockers in Melanoma | SpringerLink [Internet]. [cited 2021 Nov 9]. Available from: https://link.springer.com/article/https://doi.org/10.1007/s11481-019-09876-9

27. Katsarelias D, Eriksson H, Mikiver R, Krakowski I, Nilsson JA, Ny L, et al. The effect of beta-adrenergic blocking agents in cutaneous melanoma-a nationwide Swedish population-based retrospective register study. Cancers. 2020;12(11):E3228.

28. Afra TP, De D. Topical timolol for postacne erythema. J Am Acad Dermatol. 2021;84(6):e255–6.

29. Kimwattananukul K, Noppakun N, Asawanonda P, Kumtornrut C. Topical 0.5% timolol maleate significantly enhances skin-barrier restoration after fractional carbon dioxide laser treatment for acne scars. Lasers Surg Med. 2021;53(5):610–5.

30. Enoshiri T, Naitoh M, Yamawaki S, Kawaguchi A, Aya R, Noda K, et al. β-adrenergic receptor blockers reduce the occurrence of keloids and hypertrophic scars after cardiac device implantation: a single-institution case–control study. Plast Reconstr Surg. 2017;139(5):1248–56.

31. Abdelmaksoud A, Bonamonte D, Giudice G, Filoni A, Vestita M. Topical 1% propranolol in liposomal gel: a new adjuvant tool for chronic leprosy ulcers. Open Dermatol J [Internet]. 2018 May 31 [cited 2021 Nov 9];12(1). Available from: https://opendermatologyjournal.com/VOLUME/12/PAGE/59/FULLTEXT/

32. Dabiri G, Tiger J, Goreshi R, Fischer A, Iwamoto S. Topical timolol may improve overall scar cosmesis in acute surgical wounds. Cutis. 2017;100(1):E27–8.

33. Vestita M, Bonamonte D, Filoni A. Topical propranolol for a chronic recalcitrant wound: topical propranolol for a chronic recalcitrant wound. Dermatol Ther. 2016;29(3):148–9.

34. Vestita M, Filoni A, Bonamonte D, Annoscia P, Giudice G. Abstract: topical 0.5% timolol for chronic refractory wounds an observational prospective study. Plast Reconstr Surg Glob Open. 2017;5(9):21.

35. Rai AK, Janani K, Rai R. Efficacy of topical timolol versus saline in chronic venous ulcers: a randomized controlled trial. J Cutan Aesthetic Surg. 2020;13(1):18–23.

36. Pawar M. Topical timolol in chronic, recalcitrant fissures and erosions of hand eczema. J Am Acad Dermatol. 2021;84(3):e125–6.

37. Pawar MK. Treatment of painful and deep fissures of the heel with topical timolol. J Am Acad Dermatol. 2021;85(1):e3-4.

38. Li YF, Chen XY, Lei TC. Inhibitory effect of timolol on topical glucocorticoid-induced skin telangiectasia. Mol Med Rep. 2018;18(3):2823–31.

39. Abdelmaksoud A, Filoni A, Giudice G, Vestita M. Classic and HIV-related Kaposi sarcoma treated with 0.1% topical timolol gel. J Am Acad Dermatol. 2017;76(1):153–5.

40. FDA Approves Pierre Fabre's Hemangeol for Infantile Hemangioma [Internet]. [cited 2021 Nov 10]. Available from: https://www.fdanews.com/articles/163160-fda-approves-pierre-fabres-hemangeol-for-infantile-hemangioma

41. Farshchian M, Potts GA. Transient hypertriglyceridaemia associated with propranolol for treatment of infantile hemangioma. Australas J Dermatol. 2021;62(4):e580–1.

42. Hartmann F, Lockmann A, Himpel O, Kühnle I, Hensen J, Schön MP, et al. Combination therapy of oral propranolol and combined Nd:YAG/pulsed dye laser therapy in infantile hemangiomas: a retrospective analysis of 48 treated hemangiomas in 30 children. JDDG J Dtsch Dermatol Ges. 2020;18(9):984–93.

43. Chaturvedi K, Steinberg JS, Snyder CS. Cost-effectiveness of treating infantile haemangioma with propranolol in an outpatient setting. Cardiol Young. 2018;28(10):1105–8.

44. Putterman E, Wan J, Streicher JL, Yan AC. Evaluation of a modified outpatient model for using propranolol to treat infantile hemangiomas. Pediatr Dermatol. 2019;36(4):471–6.

45. Frongia G, Byeon JO, Arnold R, Mehrabi A, Günther P. Cardiac diagnostics before oral propranolol therapy in infantile hemangioma: retrospective evaluation of 234 infants. World J Pediatr WJP. 2018;14(3):254–8.

46. Shi H, Song H, Wang J, Xia L, Yang J, Shang Y, et al. Ultrasound in assessing the efficacy of propranolol therapy for infantile hemangiomas. Ultrasound Med Biol. 2014;40(11):2622–9.

47. Kagami S, Kaneko M, Kishi A, Katori T. Prolonged growth of infantile hemangioma after pulsed dye laser and oral propranolol treatment. J Dermatol. 2018;45(9):1109–12.

48. Filoni A, Ambrogio F, De Marco A, Pacifico A, Bonamonte D. Topical beta-blockers in dermatologic therapy. Dermatol Ther. 2021;34(4): e15016.

49. Prabha N, Chhabra N, Arora R. Beta-blockers in dermatology. Indian J Dermatol Venereol Leprol. 2017;83(3):399–407.

50. Chen L, Tsai TF. The role of β-blockers in dermatological treatment: a review. J Eur Acad Dermatol Venereol JEADV. 2018;32(3):363–71.

51. Léaute-Labrèze C, Boccara O, Degrugillier-Chopinet C, Mazereeuw-Hautier J, Prey S, Lebbé G, et al. Safety of oral propranolol for the treatment of infantile hemangioma: a systematic review. Pediatrics. 2016;138(4): e20160353.

52. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet Lond Engl. 2017;390(10089):85–94.

53. Mellerio JE. Beta blockers for infantile haemangiomas: where should we go from here? Br J Dermatol. 2019;180(3):450–1.

54. Al-Haddad C, El Salloukh NA, El Moussawi Z. β-blockers in the treatment of periocular infantile hemangioma. Curr Opin Ophthalmol. 2019;30(5):319–25.

55. Oberlin KE. Expanding uses of propranolol in dermatology. Cutis. 2017;99(4):E17–9.

56. Kim KH, Choi TH, Choi Y, Park YW, Hong KY, Kim DY, et al. Comparison of efficacy and safety between propranolol and steroid for infantile hemangioma: a randomized clinical trial. JAMA Dermatol. 2017;153(6):529–36.

57. Hu L, Zhou B, Huang H, Chang L, Qiu Y, Ma G, et al. Effects of systemic propranolol treatment on physical growth of patients with infantile hemangiomas. J Dermatol. 2016;43(10):1160–6.

58. Zaher H, Rasheed H, El-Komy MM, Hegazy RA, Gawdat HI, Abdel Halim DM, et al. Propranolol versus captopril in the treatment of infantile hemangioma (IH): a randomized controlled trial. J Am Acad Dermatol. 2016;74(3):499–505.

59. Baselga E, Dembowska-Baginska B, Przewratil P, González-Enseñat MA, Wyrzykowski D, Torrelo A, et al. Efficacy of propranolol between 6 and 12 months of age in high-risk infantile hemangioma. Pediatrics. 2018;142(3): e20173866.

60. Kagami S, Kaneko M, Katori T. Thirty-two Japanese cases of infantile hemangiomas treated with oral propranolol. J Dermatol. 2018;45(6):719–22.

61. Kaneko T, Sasaki S, Baba N, Koh K, Matsui K, Ohjimi H, et al. Efficacy and safety of oral propranolol for infantile hemangioma in Japan. Pediatr Int Off J Jpn Pediatr Soc. 2017;59(8):869–77.

62. Comparing the Clinical, Radiologic and Biochemical Effectiveness of Atenolol and Propranolol in the Treatment of Infantile Hemangioma - A Randomized Controlled Trial by Raihan Ashraf, Rahul Mahajan, Muneer Abas, Sanjeev Handa, Anindita Sinha, Dipankar De, Naresh Sachdev:: SSRN [Internet]. [cited 2022 May 30]. Available from: https://

papers.ssrn.com/sol3/papers.cfm?abstract_id=3353380

63. Lahrichi A, Hali F, Baline K, Fatoiki FZE, Chiheb S, Khadir K. Effects of propranolol therapy in Moroccan children with infantile hemangioma. Arch Pediatr Organe Off Soc Francaise Pediatr. 2018;25(8):449–51.

64. Tan JMC, Lim HW, Koh MJA. Oral propranolol for the treatment of infantile haemangiomas in Singapore. Singapore Med J. 2021;62(3):139–42.

65. Treatment with propranolol for infantile hemangiomas: single-center experience—Turhan. J Cosmet Dermatol Wiley Online Library 2016 [Internet]. [cited 2021 Nov 10]. Available from: https://onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1111/jocd.12220

66. Tognetti L, Pianigiani E, Ierardi F, Cartocci A, Fiorani D, de Quattro M, et al. A new clinical and dermoscopic monitoring of infantile hemangiomas treated with oral propranolol. Dermatol Ther. 2020;33(6): e14283.

67. Schwartz T, Faria J, Pawar S, Siegel D, Chun RH. Efficacy and rebound rates in propranolol-treated subglottic hemangioma: a literature review. Laryngoscope. 2017;127(11):2665–72.

68. Mannschreck DB, Huang AH, Lie E, Psoter K, Puttgen K. Topical timolol as adjunct therapy to shorten oral propranolol therapy for infantile hemangiomas. Pediatr Dermatol. 2019;36(3):283–9.

69. Oral propranolol combined with topical timolol for compound infantile hemangiomas: a retrospective study | Scientific Reports [Internet]. [cited 2022 May 30]. Available from: https://www.nature.com/articles/srep19765#Tab2

70. Yu X, Zhang J, Wu Z, Liu M, Chen R, Gu Y, et al. LUMBAR syndrome: A case manifesting as cutaneous infantile hemangiomas of the lower extremity, perineum and gluteal region, and a review of published work. J Dermatol. 2017;44(7):808–12.

71. Seo BH, Kim DH, Suh HS, Choi YS. Facial flushing and erythema of rosacea improved by carvedilol. Dermatol Ther. 2020;33(6): e14520.

72. De Giorgi V, Grazzini M, Benemei S, Marchionni N, Geppetti P, Gandini S. β-Blocker use and reduced disease progression in patients with thick melanoma: 8 years of follow-up. Melanoma Res. 2017;27(3):268–70.

73. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009) — Centre for Evidence-Based Medicine (CEBM), University of Oxford [Internet]. [cited 2022 May 30]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009

74. Khan M, Boyce A, Prieto-Merino D, Svensson Å, Wedgeworth E, Flohr C. The role of topical timolol in the treatment of infantile hemangiomas: a systematic review and meta-analysis. Acta Derm Venereol. 2017;97(10):1167–71.

75. Chen QY, Chang L, Qiu YJ, Ying HR, Chang SJ, Zhang Y, et al. Comparison of the efficacy between topical timolol and pulsed dye laser in the treatment of ulcerated infantile haemangiomas: a randomized controlled study. J Eur Acad Dermatol Venereol JEADV. 2021;35(4):e303–5.

76. Ying H, Zou Y, Yu W, Qiu Y, Ma G, Chang L, et al. Prospective, open-label, rater-blinded and self-controlled pilot study of the treatment of proliferating superficial infantile hemangiomas with 0.5% topical timolol cream versus 595-nm pulsed dye laser. J Dermatol. 2017;44(6):660–5.

77. Gan LQ, Wang H, Ni SL, Tan CH. A prospective study of topical carteolol therapy in Chinese infants with superficial infantile hemangioma. Pediatr Dermatol. 2018;35(1):121–5.

78. Mashiah J, Kutz A, Rabia SH, Ilan EB, Goldberg I, Sprecher E, et al. Assessment of the effectiveness of topical propranolol 4% gel for infantile hemangiomas. Int J Dermatol. 2017;56(2):148–53.

79. Neri I, Baraldi C, Balestri R, Piraccini BM, Patrizi A. Topical 1% propranolol ointment with occlusion in treatment of pyogenic granulomas: an open-label study in 22 children. Pediatr Dermatol. 2018;35(1):117–20.