Topical timolol in dermatology

infantile haemangiomas and beyond

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Topical timolol in dermatology: infantile hemangiomas and beyond

Running head: Timolol in dermatology

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What's already known about this topic?

- Timolol is a non-selective beta-blocker widely used for treatment of glaucoma
- Systemic beta-blockers (propranolol) have revolutionised treatment of infantile haemagiomas
- Topical timolol is of theoretical benefit for a range of dermatological conditions

What does this study add?

- Off-license dermatological indications for topical timolol include infantile haemangiomas, Kaposi's sarcoma, ulceration, promotion of wound healing, acne and rosacea
- Topical timolol for dermatological indications appears to be safe (to date) with reported adverse reactions mostly been localised in nature
- Larger studies are needed to corroborate safety data and efficacy compared to conventional treatments

Learning points

1. Timolol is a non-selective beta blocker, used in dermatology for its vasoconstrictive, angiogenesis blockade and wound healing properties.

2. Timolol has been used for infantile haemangiomas treatment widely, and now interest has resurged as less invasive, low-cost and simple treatment particularly in PG, KS, chronic wound healing, post-surgical wounds, acne, rosacea, eczema, red scrotum syndrome, heel fissures, post-traumatic reactive angioendotheliomatosis and tufted angioma.

3. Timolol has a low adverse effect profile, with few incidences of systemic absorption, especially when mucous membranes and ulcerated area are avoided.

4. Timolol hydrogel 0.1% has shown less systematic absorption potential, with the same efficacy compared to 0.5% timolol aqueous solution.

Abstract

Timolol, a non-selective β-adrenergic receptor blocker, is well-tolerated and is becoming increasingly popular in dermatology especially after its use in the management of infantile hemangiomas. Its effects are mainly due to vasoconstriction, inhibition of angiogenesis and keratinocyte migration promotion for re-epithelialization and wound healing. We review the evidence behind the use of timolol in several dermatological conditions including infantile hemangiomas, pyogenic granulomas, Kaposi's sarcoma, chronic wound healing, post-surgical wounds, acne vulgaris, rosacea, eczema and red scrotum syndrome.

Introduction/Background

β-adrenergic receptor blockers are commonly used systemically in the management of many cardiovascular diseases and more recently recognized for treatment of infantile haemangiomas. We review the evidence supporting the use of topical timolol, a non-selective beta-adrenergic receptor antagonist, for an array of dermatological indications.

Mechanism of action

Timolol is a non-selective beta-adrenergic receptor antagonist of moderate lipid solubility, widely used for glaucoma management. Timolol decreases the sympathetic stimulation of β receptors by competing with catecholamines. Blockade of vascular β-adrenergic receptors, inhibits tumour proliferation and angiogenesis via down-regulating vascular endothelial growth factor. Furthermore, it enhances keratinocyte migration by reducing phosphatase 2A phosphorylation and increases the cellular migration to the negatively charged centre of the injured wound.[1]

Infantile hemangiomas

Topical timolol has been used as a less invasive alternative to systemic propranolol for infantile haemangiomas (IH). A meta-analysis (887 patients from 10 studies, 0.5% timolol used in 90% studies) showed significantly improved response rate when compared to the controls(p<0.00001) during treatments of two to six months duration (Table 1).[2] Topical timolol has been proposed as first line treatment for deep lesions and functionally compromised patients.[3] Five children experiencing purely deep lesions and amblyogenic features showed complete regression after using topical timolol maleate 0.5% solution, three drops twice daily for mean duration 10 months.[4] Low concentration timolol gel (0.1%) five times daily; resulted in mean improvement in global assessment score of 2.56 (range 1.67-3) noticed in all 25 children with IH (mean age 30 weeks, range 12-68 weeks).[5]

Pyogenic granuloma

Timolol has been used as a topical alternative to procedural interventions for pyogenic granulomas (PGs). Amongst 17 patients with ocular PGs (mean age 23 years; range 3-67 years), 88% demonstrated complete lesion resolution with 0.5% timolol solution given twice daily for a period between two to five weeks with no recurrences noted after mean 9.47 months. Two patients needed surgical excision after 6 weeks of no response.[6] A separate case series suggested that efficacy of timolol is variable after two thirds of patients required electrosurgery as a result of partial (2/10 cases) or no (4/10 cases) response. Efficacy of timolol was proposed to be better in PGs of recent onset and higher vascularity.[7]

Kaposi's sarcoma

Where tumours are localised, topical timolol has been used as a treatment for Kaposi's sarcoma (KS) due to its anti-angiogenic properties and possible lysis of viral-infected cells. Most of the published data illustrated partial to complete resolution when administrating 0.5% or 0.1% timolol strength in HIV negative patients.[8] In the two cases of HIV negative KS patients treated with 0.5% timolol solution twice daily for a twelve-week period, lesions showed significant improvement after 6 and 12 weeks with no recurrences after 20 months.[9] A HIV positive KS patient, 0.1% timolol gel applied twice daily induced resolution within 6 weeks with no recurrence after four months.[10]

Chronic recalcitrant wound healing

Topical timolol facilitates wound healing through the promotion of keratinocyte migration. Thirty nine patients with 55 chronic wounds of various aetiologies (including venous insufficiency, vasculitis, pressure sores, trauma) recalcitrant to conventional treatments were treated with topical timolol 0.5% every dressing change (frequency from twice daily to alternate days). Notably, 34/55 wounds had completely healed with 89.5 days median treatment duration and only 6/55 showed no improvement in 76 median treatment duration days. Optimal healing was proposed to be achieved with compression and more frequent application of timolol.[11] A case-control study with 60 patients with chronic diabetic and venous ulcers showed the timolol group had an increased percentage improvement in the ulcer area.[12] Two children with junctional epidermolysis bullosa with chronic wounds of the neck fold and nailbed were treated successfully with topical timolol.[13]

Post-surgical wounds

Topical timolol promotes reepithelisation of iatrogenic wounds. Following successful use in two patients, Waldman *et al.* suggested 0.5% timolol ophthalmic gel forming solution be used twice daily until complete resolution as a second line treatment for wounds refractory to standard therapy. A patient with hypergranulation refractory to daily nonadherent gauze dressings and both oral and topical antibiotics for several months, showed complete settling of hypergranulation and surgical site re-epithelialization after nine days.[14] A randomized control trial (RCT) of six patients with acute surgical scars showed patients applying topical timolol group had higher visual analogues scores (VAS) and enhanced cosmesis compared to application of saline control (mean VAS: timolol 6.5 versus control 2.5; $p<0.05$).[15] Topical timolol has been reported to be helpful for patients with surgical defects following Mohs surgery[16] and a patient with a slowly healing wound following radiotherapy.

A lady with a refractory chronic mid-back wound due to thoractomy for previous cardiac surgery was treated with 0.5% timolol drops three to four drops daily with complete epithelilaization seen in eight weeks.[17] Topical timolol has proved to be useful in restoring skin-barrier function following fractional CO2 laser therapy for acne. [18]

Acne vulgaris and rosacea

Timolol through its β-blocking properties both suppresses inflammatory mediators and induces vasoconstriction which can be helpful in reducing disease severity and erythema in chronic inflammatory skin diseases such as acne and rosacea.[19]

Reduction in erythematotelangectatic rosacea was seen in an 8-patient trial; however at 16 weeks erythema recurred.[20] A case-study looking at post-acne erythema and hyperpigmentation showed improvement with topical timolol on subjective dermoscopic evaluation following three months of therapy.[21]

Miscellaneous

A patient with recalcitrant fissures and erosions caused by eczema showed complete healing one week following application of topical timolol on.[22]

A patient with red scrotum syndrome resistant to other treatments showed response within two weeks after using topical timolol.[23] Timolol 0.5% ophthalmic solution has shown symptom relief and significant healing of painful and deep heel fissures after two weeks of therapy.[24] A patient with post-traumatic reactive angioendotheliomatosis (PRA) used timolol maleate 0.5% ophthalmic solution and demonstrated a full resolution for all lesions with mild scarring after six weeks.[25] Four

months of 0.5% timolol gel-forming solution for a four-month-old child with tufted angioma resulted in almost complete resolution.[26]

Adverse effects and safety profile

Topical timolol is generally well tolerated with few adverse events (Es); systemic absorption could occur particularly if applied to mucous membranes and ulcerated areas. Timolol applied as eye drops could enter the nasolacrimal duct and reach the nasal mucosa, leading to 80% systemic absorption and the avoidance of first pass metabolism. As a non-selective beta blocker, timolol could theoretically cause bradycardia, hypotension, bronchospasm induction, fatigue, hyperglycaemia, AV block, syncope, worsening congestive heart failure and sleep disturbance.[27,28]

Timolol hydrogel 0.1% may be associated with fewer systemic AEs compared to 0.5% timolol aqueous solution with comparable efficacy. Lin et al. conducted a meta-analysis involving 2098 patients and concluded that topical timolol is associated with low incidence of AEs, and most of them are classed as localized including, desquamation and erythema.[29] Several cases of allergic contact dermatitis have been reported in the literature after the application of topical timolol.[30] One child out of sixty experienced insomnia and shortness of breath upon using 0.5% topical timolol maleate solution twice daily.[31]

Conclusion

Topical timolol is a low-cost, effective and simple treatment with few AEs reported in dermatology patients. Larger RCTs and rigorous meta-analyses are needed to establish the optimal concentrations and frequency of application and confirm the safety profile of this off-licence medication. Dermatologists should consider use of topical timolol, in patients with haemangiomas and PGs where surgical therapy is undesirable and recalcitrant chronic and surgical wounds.

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Table 1 Uses of Topical Timolol in dermatology

Indications & references	Study design	Number of patients, *n*	Treatment period	Dose & frequency	Outcomes & adverse effects
Infantile hemangiomas Zheng L & Li Y, 2018[2]	Meta-analysis including 10 studies. 5 randomized controlled trials, 3 prospective cohort studies and 2 retrospective cohort studies. The studies indicated moderate and high quality with moderate and acceptable bias risk.	887 infants with hemangioma. 603 with timolol group and 284 with the control group. 843 infants with superficial lesion; 40 infants with mixed lesion; 4 infants with deep lesion	varies from 2 to 6 months	9 studies used 0.5% timolol. Timolol was prescribed twice daily in 5 studies	Confirmed timolol monotherapy was superior on response rate and AE to placebo, observation and laser, yet when compared to propranolol there was no significant difference in the response rate. RRs with 95% confidence intervals. A random effect model was utilized. 8 trials compared the response rate of timolol to laser, observation, placebo or propanol with statistically significant heterogeneity ($P < 0.00001$, $I^2 = 83\%$) and significant response rate (RR = 2.86, 95% CI 1.31–6.24) when compared to controls, but no significant difference when compared to propanol (RR = 0.99, 95% CI 0.70–1.42). 9 trials reported adverse effects when comparing timolol to the controls with statistically difference in adverse effects (RR = 0.21, 95% CI 0.05–0.97) and insignificant heterogeneity ($P = 0.27$, $I^2 = 23\%$).
Painter SL & Hildebrand GD, 2016[4]	Retrospective and consecutive case series.	5 children with deep and periocular IH causing astigmatism, ptosis or change in head posture.	Timolol was used until full regression occurs.	Timolol maleate 0.5% solution. 3 drops rubbed by the parent twice every day until	All the affected children had regression in the lesion and improvement in the amblyogenic risk factors during the first 2 weeks. Timolol was continued until full regression occurred. Measurements and examinations were subjective.

			Ranges from 6 to 18 months. Ten months mean duration.	lesion has regressed fully.	Patients after cessation, had at least 8-month period of follow up in case a rebound occurred. In all cases no side effects were noted, but only one case had a mild wheeze due to a mistake in timolol application into the eye.
Semkova K & Kazandjieva J, 2013[5]	Prospective study	25 patients; 15 girls and 10 boys had 39 nonulcerated superficial localized His.	6 months	Timolol 0.1% gel. One drop of the gel per cm^2 five times daily.	Treatment efficacy evaluation was carried out at 4-week intervals via two separate investigators and concordance between them was calculated using the intraclass correlation coefficient (ICC). After the first 4 weeks, the consistency of all lesions moved from tense to soft. All IHs showed improvement giving a mean score of 2.56 (range 1.67-3) and the mean percentage change from baseline is 85% (range 55.6-100%). ICC for inter-rater. Reliability was 0.81. Complete clearance was noted in 3 children with plaque hemangiomas during the early phase of proliferation and also one child during the involuting phase. Timolol application during the proliferation phase was found superior to the involution phase giving a mean GAS of 2.61 (87%) and 2.21 (73.7%), respectively. No adverse effects were noted. No fluctuations in the vital signs were noted for the children with larger or multiple lesions who had higher quantities of the drug.

PYOGENIC GRANULOMA (PG) **DEMARIA LN *ET AL.*, 2018[6]**	Retrospective interventional case series.	17 ocular PGs patients; 9 females and 8 males. Seven of the patients were children; less than 18 years.	6 weeks the whole study. Mean treatment duration for a complete resolution is 3.07 weeks (range from 2-5 weeks)	Timolol 0.5% solution. Applied twice daily.	Mean lesion size before treatment was 5.06×6.06mm. 13 patients had sessile (76%) and 4 patients presented with pedunculated lesions (24%). Fifteen patients showed a complete lesion resolution for a mean treatment duration of 3.07 weeks (range, 2-5 weeks) with no recurrences in a mean follow period of 9.47 months (range,6-27 months). Two patients had surgical excision after failing to present a response in a 6-week period. The cases had palpebral conjunctiva PG related to chalazion larger considerably than the other cases with the largest dimension of 18mm for both cases. No side effects were noted.
Gupta D *et al.,* 2016[7]	Case series	10 patients	4 months. A complete resolution occurred in 4 patients within 3-24 days. At the end of 3 months 5 patients had electrosurgery and one patient at the end of 6	Timolol 0.5% ophthalmic solution. Applied 4 times, daily in 2 drops per dose (0.05ml or 0.25 mg per drop).	The efficacy of the treatment was determined by considering a complete response when the whole lesion disappears, a partial response when reduction in lesions number and/or size occur and no response when no reduction is noted. Four patients experienced a complete response during 3-24 days and no recurrence noted within 3 months of follow up. Three patients each presented with no response or partial response. Then, electrosurgery was performed to remove the lesions in five patients at the end of 3 months and one

			months.		patient had electrosurgery at the end of 6 months. No adverse effects were noted. No abnormality reported in blood pressure, blood glucose, ECG and heart rate.
Kaposi's sarcoma (KS) - HIV negative Meseguer-Yebra C *et al.,* 2015[9]	Case series	2 patients	12 weeks	0.5% timolol maleate solution. Applied twice daily, 1 or 2 drops for every lesion with gentle massage and no occlusion.	Both patients had follow up visits at 0, 2, 6 and 12 weeks. Case 1 for a 78-year-old man showed significant changes after 2 weeks of treatment and the lesion changed to flattened and crusty lesion, and at 6 weeks of treatment the lesion remained as a smaller erythematous macule. At the end of the 12 weeks, lesion was excised and no evidence of KS was detected using HHV-8 immunohistochemical stain. No reoccurrence after 22 months of follow-up. Case 2 for a 94-year-old female showed reduction in size and the crusty appearance appeared during the first weeks of treatment and at the 12th week all 3 lesions presented as erythematous macules. Twenty months of follow up showed no recurrence. No side effects were noted for both cases.
Kaposi's sarcoma (KS) - HIV positive Abdelmaksoud A *et al.,* 2017[10]	Case series	4 patients. 3 cases with classic KS, and 1 case with HIV positive KS.	The 3 classic KS cases showed full resolution of the lesions in 4 to 5 weeks.	0.1% timolol gel. Twice daily administration until lesion is resolved. In the HIV positive case, timolol was withdrawn as a	The 3* cases of classic KS showed complete lesion resolution and disappearance of edema and pain within 4-5 weeks and no side effects for 6-10 months of follow up. HIV positive case improved significantly by the end

			The HIV positive case continued timolol treatment to 6 weeks only.	precautionary procedure.	of the 6th week. During the 5th week of treatment, patient experienced asthenia, unexplained fever, and failure to systematic antibiotic response. The patient was positive for tuberculosis and HIV with 360 cells/mm^3 CD4 cell count. Timolol was withdrawn and patient started emtricitabine/tenofovir disoproxil fumarate combination in addition to efavirenz once daily by the end 8th week. No signs recurrence or spreading were noted during the 4 months follow up. The highly active antiretroviral therapy might have contributed to the maintenance of lesion remission, timolol 0.1% gel was the only drug used in the first 6 weeks supporting the therapeutic efficacy of timolol. *1 patient was having oral bisoprolol 10mg/d during the treatment course.
Chronic recalcitrant wound healing – (venous insufficiency, vasculitis, pressure sores, trauma) Cahn BA *et al.,* 2020[11]	Multi-center retrospective case-series study	39 patients; 32 males and 7 females with various chronic wounds etiologies including: venous leg ulcers, truamtic wounds, pyoderma gangrenosum, diabeteic foot ulcer, malignancy (non-HIV KS), radiation dermatitis, post-surgical, post-surgical and radiation, Graft versus host disease, Neuropathic truma, pressure, vasculitis,	Healed group: 89.5 days median treatment duration. Decreasing wound area group: 122 days median treatment duration. 8 were still receiving treatment at the	0.5% timolol maleate applied for at least 4 weeks. Timolol with used in addition to standard of care therapy. 1 drop per cm^2 of wound area instilled with dressing. Dressing changes occur twice daily, once daily or every other day. Some	Authors reported healing criteria as: healing when complete re-epithelialization of the wound and closure occur, improved when wound size decreases and worsening when wound size area increases. 34 wounds healed, 15 wounds decreased in wound area and 2 venous leg ulcers increased their wound area. 4 wounds remained unchanged. healed group: median healing rate was -0.25cm^2/week. Most of the wounds had timolol

		bullous pemphigoid, compulsive skin picking.	time of analysis. Increasing wound area group: 157 days median treatment duration. No change in wound area group: 76 days median treatment duration.	patients had continuous application by a delivery system.	applied daily. 3 out of 34 healed wounds had wounds occurring a location different than the leg (1 diabetic foot ulcer, 1 abdominal post-surgical wound). Etiologies are mainly venous leg ulcers and traumatic wounds. Decreasing wound area group: median healing rate was -0.24cm^2/week. Median wound size decreased by 62%. Majority of the wounds occurred on the leg (n=11), but 4 occurred in different locations for example the scalp, abdomen, and foot. The major etiology in this subgroup include venous leg ulcer. Increasing wound area group: median rate of wound area increase was 0.17cm^2/week. Median percentage increase in wound area was 193%. All etiologies were venous leg ulcers. No change in wound area group: Four wounds remained unchanged including traumatic, radiation dermatitis, bullous pemphigoid and compulsive skin picking (difficult to evaluate due to self-excoriations). No adverse effects were reported due to timolol usage.
Chronic diabetic and venous ulcers Thomas B *et al.,* 2017[12]	case-control study. prospective and nonrandomized single-center	60 patients with chronic leg ulcers due to venous insufficiency or diabetes of less than 6 weeks in	12 weeks	0.5% timolol maleate, one drop applied for each 2 cm of the wound perimeter every day in addition to the	At 0, 4, 8 and 12 weeks, the ulcer area was calculated via plotting ulcer perimeter on graph paper and the area was measured manually. The change in ulcer area in percentage was used to

	study.	duration.	conventional therapy (antibiotics, glycemic control, absorbent dressing every 2 days unless it was heavily soaked, devitalized tissue débridement if required). Timolol was dried before dressing placement.	assess the healing rate at 4, 8 and 12 weeks. Timolol group had 24.04, 27.39, and 40.76 mean percentage change in ulcer area at 4, 8, and 12 weeks, while the control had 12.98, 14.58, and 16.52. The healing rate with timolol group is better and there is a statistically significant difference P value < 0.05 including all the three means. Timolol group had 25.29, 43.77, and 61.79 percentage change of the ulcer area at 4, 8, and 12 weeks, while the control had 1.92, 22.40, and 29.62. Repeated-measures mixed analysis of variance was used and indicated that across the three time points was significant difference $F(1.25,72.56) = 94.49$ ($P < .001$), and the study group and the control group in the ulcer area percentage change had significant differences $F(1,58) = 14.41$ ($P < .001$) Only 1 venous insufficiency patient and 3 diabetic patients in the timolol group had a complete healing at the end of study period (12 weeks). No full healing in control group. No ulcer recurrences were noted for study period. No significant difference was revealed by the study in the rate of healing between nonsmokers and smokers or alcohol consumption. In the timolol

					group, no difference in healing rate was noted by gender. The healing rate for chronic diabetic ulcer patients and chronic venous patient in both the study and control groups was not different significantly. No major adverse effects were reported. Only three patients mentioned itchiness around the ulcers occasionally.
Junctional epidermolysis bullosa (JEB) Chiaverini C *et al.,* 2016[13]	Case series	2 patients; both are 1 year old patients with generalized intermediate JEB subtype. Patient 1 had nail bed chronic wound and patient 2 had neck fold chronic wounds.	Patient 1 with nail bed chronic wounds had 3 weeks treatment course. Patient 2 with neck fold chronic wounds had 8 weeks treatment	Topical timolol 0.5%. Twice daily application 2-3 LP eye drops with occlusion.	Patient 1 with nail bed chronic wound had 3 weeks of 2 drops timolol therapy and obtained 100% healing. Patients 2 with neck fold chronic wound had 8 weeks of timolol therapy and obtained 80% healing. Parents reported no adverse effects.
Refractory Hypergranulation Waldman RA *et al.,* 2019[14]	Case series	2 patients	Up to 14 days (patient 1) or until complete resolution occurs (9 days for patient 2)	Timolol maleate ophthalmic gel forming solution 0.5% twice daily in addition to normal routine wound care and daily dressing changes.	Patient 1: Resolution of hypergranulation and surgical sites re-epithelialization with 2 weeks of timolol therapy after 6 weeks refractory hyperregulation to routine wound care and topical silver nitrate. Patient 2: Resolution of hypergranulation and surgical sites re-epithelialization with 9 days of timolol therapy after several months a traumatic injury refractory hyperregulation to topical and oral

					antibiotics and nonadherent sterile gauze dressings every day. No adverse effects were noted that require discontinuation of timolol therapy.
Overall scar cosmesis in acute surgical wounds Dabiri G *et al.,* 2017[15]	Randomized controlled trial (RCT)	9 enrolled in the study but 6 completed the study. 3 patients in the study group and 3 in the control.	13 weeks or less if healed earlier.	Not mentioned?! Timolol (maybe ophthalmic solution). Dose is not mentioned. Timolol is applied and then 40 mm Hg compression stockings were worn.	The authors defined the healed wound as a wound without exudate, and with complete reepthelialization and stability for 1 week. (VAS) visual analog scale is the subjective scar assessment used to calculate scar cosmesis. 2×2 cm was the average wound size with a depth of 1mm. The VAS was measured by outside blinded dermatologist and results showed timolol treated wounds had more cosmetically favorable scars compared to the control (mean [SD]: 6.5 [0.9] vs 2.5 [0.7]; P<.05). The paper didn't mention adverse effects.
Recalcitrant irradiated surgical (Mohs surgery) scalp wound Beroukhim K & Rotunda AM, 2014[16]	Case report	1 patient	4 months	3 to 4 drops of 0.5% topical timolol maleate distributed to the entire wound twice daily, but then reduced to once daily, every other, or every third day due to mild irritant dermatitis.	Patient's surgical defect following 2 stages of Mohs surgery was 10 × 11 cm with uncovered bone pitting. Patient initially followed wound care routine consisting of soap and water washing of the scalp daily or every other day and using petroleum jelly and a nonadherent bandage to cover the wound. After 3 years of routine wound care, modest improvement with poor vascularized and friable

				Timoptic ophthalmic solution.	granulation tissue persistence over central zone of the pitted bone. The Recalcitrant irradiated surgical (Mohs surgery) scalp wound had a flattening of the granulation tissue and nearly complete reepithelialization after 2 months of timolol therapy and wound care (consists of soap and water washing of the scalp daily or every other day and using petroleum jelly and a nonadherent bandage to cover the wound). After 4 months of timolol therapy and wound routine, a complete reepithelialization of the entire wound was noted. Adverse effects: mild contact dermatitis, mild erythema.
Refractory chronic mid-back wound Tang JC *et al.,* 2012[17]	Case report	1 patient with large refractory wound on her left mid-back	8 weeks	3 to 4 drops of every day of topical timolol drops 0.5% to the wounds and the wound were covered via a soft silicon dressing.	A complete and rapid epithelization for the 43-year-old women had refractory a 26-cm^2 defect with 3.5 cm depth thoracic back wound with an underlying 6-× 9 4-cm ulcer with red-pink granulation tissue. No significant adverse effects were noted and treatment was well tolerated.
Fractional CO_2 laser therapy ($AFCO_2$) Kimwattananukul K *et al.,* 2021[18]	Split-face double blind and randomized placebo-controlled trial	25 patients with history of atrophic scars for at least 3 months. Mean age (SD) is 31.4 (5.2) years. Fitzpatrick skin phototype IV constitutes 80% of the	7 consecutive days	10-15 drops of 0.5% topical applied twice daily immediately after the laser procedure. A moisturizer and sunscreen were also used.	Follow up visits includes 48, 96 and 168 hours post Fractional CO2 laser therapy. All 25 patients completed the study. Patients' adherence was evaluated via measuring solution bottles at baseline and at end of the study.

		participants' skin.	There was no significant difference in timolol and normal saline quantities during the study period (4.14 vs. 4.25 g, respectively; P = 0.26). After 48 hours of post-$AFCO_2$ therapy until the end of study, timolol treated side had significantly higher skin hydration level compared to normal saline treated side (P<0.001). TEWL (transepidermal water loss) levels were significantly lower at timolol treated side compared to the controls for every follow-up visit P<0.001. Colorimetry measurement showed no significant difference in skin erythema reduction between timolol and control group at all time points. No difference seen in timolol and control group regarding erythema and edema scores at 48. 96, and 168 hours after the $AFCO_2$ treatment. 96 hours post-$AFCO_2$ therapy, crusting score on showed a significant greater improvement in timolol treated side (crusting scores: 1, 19/25 [76%] and 2, 6/25 [24%]) compared to the controls (crusting scores: 1, 9/25 [36%] and 2, 16/25 [64%]) (P = 0.002). Photographs were consistent with crusting scores and indicated visually the reduction in crusting in the timolol treated cheeks throughout the study period.

					At 48h and 168h post-$AFCO_2$ treatment, timolol treated side demonstrated slightly lower pruritus and tightness scores compared to controls, yet the differences were not statistically significant. No adverse effects were reported from the patients during the study period. Six patients had mild and transient post-inflammatory hyperpigmentation in both cheeks (timolol treated cheek and control cheek)
Acne and rosacea Al Mokadem SM *et al.,* 2020[19]	Multicentric study (case series, I think?)	166 patients; 58 patients with rosacea (erythematotelangiectatic or papulopustular Rosacea) and 58 with acne (mild or moderate acne) patients.	8 weeks	4 to 8 drops of 0.5% topical timolol maleate applied every night.	For acne the global acne grading system was used. Investigator's Global Assessment (IGA) score and a rosacea clinical scale were used for rosacea. Acne group included 42 (72.4%) mild acnes and 16 (27.6%) moderate acne. After therapy, a high statistical significant decrease in papules, TLC (total lesion count), ASI (acne severity index), comedones from the baseline and pustules showed statistical significant reduction also. The means percentage improvement were 28.17% comedones, 26.81% papules, 16.05% pustules, 25.11% TLC and 23.24% ASI. Rosacea group included 10 (17.2%) mild cases, 32 (55.2%) moderate cases and 16 (27.6%) severe cases according to IGA. After therapy, 10.4% of patients demonstrated "clear" or almost clear score IGA. After therapy, 20.6% of the cases were considered severe, 34.5% moderate cases and

					34.5% mild cases compared to (27.6%, 55.2% and 17.2%, respectively) according to IGA. 55.1% of patients were considered as non-responders per IGA results. Adverse effects for both groups were mild and tolerable. Most reported adverse effect was dryness. Adverse effects also include a burning sensation, mild irritation, scaly skin, itching, stinging and erythema.
Erythematotelangectatic rosacea Tsai J *et al.,* 2021[20]	A quantitative, split-face, randomized, and rater-masked pilot clinical trial	8 patients with rosacea containing flushing and persistent erythema.	16 weeks of timolol treatment for one side of the face. The contralateral side received no treatment for the first 8 weeks and then treated the following 8 weeks.	0.5% topical timolol gel-forming solution applied twice daily.	Facial erythema was measured using tristimulus colorimetry and computer-aided image analysis (CAIA) of cross-polarized photographs from baseline and then every 4 weeks until 4 weeks after treatment stoppage. Patients asked to rate flushing from 1 “much worse” to 5 “much better” for each photobaseline visit. Four patients reported improvement with treatment. Three patients reported worsened flushing after therapy discontinuation. There is a strong correlation between colorimeter and CAIA-measured facial erythema (r = 0.71, P <.001) With the mixed-effects models, erythema decreased in both sides of the face (treated and untreated) during the early 8 weeks yet considered

					insignificant statistically. Upon subsequent therapy for both sides, improvement was seen only in the longer treated side most significantly observed at 12th week (colorimeter-20.0%, adjusted *P*= .001; CAIA -20.9%, adjusted *P* = .047) Erythema recovered at week 16 suggesting tolerance. Erythema rebound was observed after timolol discontinuation. Only one adverse event was reported which is one episode of transient lower eyelid sensitivity.
POST-ACNE ERYTHEMA AND HYPERPIGMENTATION **AFRA TP *ET AL.*, 2021[21]**	Case report	One patient	12 weeks	0.5% topical timolol maleate ophthalmic solution applied at bedtime.	Significant improvement in post-inflammatory erythema of patient's acne leaving only shallow rolling scars and no pigmentation. Evaluation was made with dermoscopy. No adverse effects were noted.
Eczema Pawar M, 2021[22]	Case report	One patient	1 week	0.5% ophthalmic timolol solution administered 2-3 drops on the fissure/erosion areas.	A patient with chronic hand eczema demonstrated healed recalcitrant fissures and erosions after one week of timolol therapy. The paper didn't mention any adverse effects.
Red scrotum syndrome Pyle TM & Heymann WR, 2019[23]	Case report	One patient	2 weeks	0.5% Topical timolol maleate gel forming solution applied twice daily.	A 48-year-old man with 2 months history of resistant red scrotum syndrome to fluconazole 200 mg, minocycline, topical nystatin-triamcinolone acetonide cream, tacrolimus 0.1% ointment and topical mupirocin 2% ointment. The patient had a trial of 6.25 mg carvedilol daily

					but without improvement. Timolol was added and the erythema and symptom resolved rapidly within 2 weeks. The patient continued carvedilol due to hypertension and symptoms of RSS returned when timolol was withdrawn. The symptoms resolved after timolol therapy restarted. The paper didn't mention adverse effects.
Deep painful heel fissures Pawar MK, 2021[24]	Case report	One patient	4 weeks	2 to 3 drops of 0.5% ophthalmic timolol solution applied over the fissures at bedtime.	After 2 weeks of timolol therapy and wearing good fitting and closed-back shoes, symptoms resolved and healed significantly. Therapy continued for another 2 weeks and no recurrence of heel fissures were noted after 4 weeks of treatment. The paper didn't mention adverse effects.
Posttraumatic reactive angioendotheliomatosis Bhatia R *et al*., 2021[25]	Case report	One patient; male patient in his 20s	6 weeks	2 drops of timolol maleate 0.5% ophthalmic solution applied 3 times daily	A complete resolution for all 7 Reactive angioendotheliomatosis (RAE) lesions with mild scarring. No lesions reoccurrence after 1 year of follow up. The paper didn't mention any adverse effects.
TUFTED ANGIOMA **BEHERA B *ET AL*., 2021[25]**	Case report	One patient; a four-month-old male.	6 months	0.5% gel-forming solution applied thrice daily and then reduced to twice daily, once daily and then stopped.	After 4 months of timolol therapy, almost a complete resolution occurred to 6 cm × 3cm circumferential unusual reddish-brown horseshoe-shaped plaque tufted angioma. Treatment dosage was reduced and then stopped over the following 2 months. No lesion recurrence after one year of treatment stoppage.

		No complain of adverse effects were reported by the parents.