Effect of Topical 0.5% Timolol Maleate After Fractional Carbon Dioxide Laser in Acne scar

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Abstract:
Skin barrier is often compromised following ablative fractional carbon dioxide laser ($AFCO_2$) therapy for acne scarring. The resultant downtime, even of a few days' duration, can be of significant concern to patients. We evaluated the efficacy and safety of topical 0.5% timolol maleate (TM) for its role in short-term restoration of the skin's biophysical properties after laser treatments.

Keywords: Timolol, Fractional Carbon Dioxide Laser, Acne scar.

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Introduction:

Timolol is a nonselective β-blocker that has been used for treating hemangioma. It causes vasoconstriction, induces apoptosis, and inhibits angiogenic factors, such as vascular endothelial growth factor (VEGF), and inflammatory mediators, such as matrix metalloproteinase (MMP)-2, MMP-9, and interleukin (IL)-6 **(1).**

Timolol is a nonselective beta-blocker available for both topical and systemic administration. Topical timolol is primarily used to reduce intraocular pressure in patients with open-angle glaucoma and ocular hypertension. Topical timolol has also been shown to effectively treat and minimize thin, superficial infantile hemangiomas. Systemic administration of timolol can be part of a regimen managing hypertension, myocardial infarction, and migraine prophylaxis. The use of timolol to treat adult atrial fibrillation is controversial**(2).**

FDA-Labeled Uses of Topical Timolol:

- Open-angle glaucoma
- Ocular hypertension

Off-Label Uses of Topical Timolol:

- Infantile hemangioma

FDA-Labeled Uses of Systemic Timolol:

- Hypertension (not first-line)
- Myocardial infarction
- Migraine prophylaxis

Off-Label Uses of Systemic Timolol:

- Atrial fibrillation (adult)

Ocular Side Effects:

- Burning
- Stinging
- Irritation
- Dryness
- Itching
- Watery eyes

- Conjunctival hyperemia
- Blurry vision

Systemic Side Effects

- Bronchospasm
- Bronchoconstriction
- Bradycardia
- Depression
- Fatigue
- Confusion
- Hair loss
- Sexual impotence
- Disorientation
- Increased low-density cholesterol levels
- Headache
- Dizziness **(3)**

Mechanism of action:

Beta-blockers can be used as monotherapy or in combination with other systemic therapies for mixed IH. Topical timolol 0.5% gel was favored over topical timolol maleate 0.1% and topical propranolol. No differences were observed in the reduction of SIH size from either oral propranolol or topical timolol maleate, with the advantage of topical administration being minimal absorption and systemic adverse effects. However, topical administration appears to have a slower onset of action (12–16 weeks). 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. However, a study by Randall A. et al. warned about their use in lesions located on mucosal surfaces and in the periocular region due to unpredictable systemic absorption **(4).**

Timolol, through its anti-inflammatory properties, might provide a new treatment option for acne and rosacea, because inflammation is known as a fundamental factor in the pathogenesis of both diseases. In addition, timolol can improve erythema and flushing in rosacea by inhibiting β-adrenergic receptors on the smooth muscles surrounding blood vessels, leading to vasoconstriction of these vessels**(4).**

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Application of 0.5% timolol after TCA-CROSS in patients complaining of acne scars was found to slightly decrease scar severity and result in a significant reduction of post-inflammatory hyperpigmentation (PIH) duration **(5).**

Topical TM application resulted in complete wound healing in a 43-year-old patient with a refractory wound on the back . In chronic leg ulcers, Thomas et al. reported that 0.5% TM application significantly improved wound healing compared with the conventional therapy, which included wound dressing and debridement, glycemic control, and antibiotics as per cultures and sensitivity, in 60 patients. For acute surgical wounds, among non melanoma skin cancer patients who underwent Mohs micrographic surgery and whose wounds healed by secondary intention, the TM-treated group showed more cosmetically favorable wound healing than the normal saline group **(6).**

The hypothesized mechanism of action of TM on wound healing relies on the findings of beta-adrenergic receptors and the

mitogen-activated protein kinase pathway (MAPK) in human keratinocytes. Chen et al. found that isoproterenol, a beta-1 and -2 adrenergic agonist, inhibited the MAPK pathway resulting in decelerated keratinocyte migration **(7)**. By blocking beta-adrenergic receptors, **Pullar et al. (7)** had demonstrated that TM promoted keratinocyte migration and enhanced re-epithelialization by increasing the extracellular-signal-regulated kinase phosphorylation in the MAPK signaling pathway **(8).**

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. No local or systemic adverse effects were reported **(9).**

A healthy and adequately functioning skin barrier is characterized by relatively high skin hydration levels and low TEWL levels. Skin hydration, measured by corneometry, represents the water content of the stratum corneum, whereas TEWL reflects the insensible loss of water from the skin. Both corneometry and TEWL measurements are very practical, sensitive, and non-invasive tools used in many studies as objective assessment modalities. AFCO$_2$ resurfacing damages the stratum corneum and epidermis, leading to a decrease in skin hydration levels and an increase in TEWL levels. Therefore, management to shorten the recovery time by restoring the skin barrier is crucial as it leads to reduced postoperative downtime **(10).**

Another report, showed an increase in the rate of wound healing caused by destructive CO_2 laser after using topical timolol. Treatment sites ablated by laser for which topical timolol 0.5% was applied demonstrated less inflammation and a significantly lower transepidermal water loss (TEWL) than ablated areas where no timolol was applied **(11).**

Moreover; timolol was found to induces apoptosis, inhibit angiogenic factors, such as vascular endothelial growth factor (VEGF), and inflammatory mediators, such as matrix metalloproteinase (MMP)-2, MMP-9, and interleukin (IL)-6. Such properties had demonstrated its potential usefulness for treating acne and rosacea**(12).**

There were no adverse events reported in our study. A systematic review of TM in the treatment of infantile hemangioma supported its safety profile. Although TM levels were detected in the serum, there were no reported systemic adverse effects even when applied to mucosal or ulcerated areas in 691 patients. Another comparative study showed no significant difference in the plasma level between wounds to which TM was applied and the eyes of glaucoma patients in whom ophthalmic preparations were applied **(13).**

To avoid measurement errors and biases in skin biophysical evaluations due to diurnal variations, we used the unit of hours, instead of days, during follow-up. Evidence showed that TEWL levels increase significantly in the evening at all sites

(forehead, forearm, upper back, and shin) and are the lowest in the morning. Although skin hydration does not show time-dependent variations, the maximal and minimal values were obtained around 4 p.m. and 10 p.m., respectively. These show significant differences in healthy skin barrier functions during the day **(14).**

References:

1. Krakowski A. C. and Nguyen T. A., (2015): "Inhibition of Angiofibromas in a Tuberous Sclerosis Patient Using Topical Timolol 0.5% Gel." Pediatrics, vol. 136, no. 3, e709–e713
2. Lazreg S. and Merad., (2018): "Efficacy and Safety of Preservative-Free Timolol 0.1% Gel in Open-Angle Glaucoma and Ocular Hypertension in Treatment-Naïve Patients and Patients Intolerant to Other Hypotensive Medications." Journal Francais d'Ophtalmologie, vol. 41, no. 10, pp. 945–954
3. Onishchenko A. L. and Isakov., (2019): [Initial combination therapy for primary open-angle glaucoma]. Vestnik Oftalmologii, 135(2), 32–38.
4. Wang X. and Feng. (2021): The efficacy and safety of topical β-blockers in treating infantile hemangiomas: a meta-analysis including 11 randomized controlled trials. Karger.Com, 237, 433–443.
5. Ghassemi M. and Shahverdi. (2022): "Efficacy and Safety of Topical Timolol 0.5% Plus Saline 0.9% Versus Each One Alone in Acne Scar Trichloroacetic Acid-CROSS Therapy: A Blinded Randomized Controlled Trial." Dermatologic Therapy, vol. 35, no. 4,
6. Thomas B. and Kurien. (2017): Topical timolol promotes healing of chronic leg ulcer. Journal of Vascular Surgery. Venous and Lymphatic Disorders, 5(6), 844–850.
7. Pullar C. E. and Rizzo. (2006): beta-Adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. The Journal of Biological Chemistry, 281(30), 21225–21235.
8. Chen J. and Hoffman. (2002): "Beta-Adrenergic Receptor Activation Inhibits Keratinocyte Migration via a Cyclic Adenosine Monophosphate-Independent Mechanism." The Journal of Investigative Dermatology, vol. 119, no. 6, pp. 1261–1268,
9. Kimwattananukul K. and Noppakun., (2021): "Topical 0.5% Timolol Maleate Significantly Enhances Skin-Barrier Restoration After Fractional Carbon Dioxide Laser Treatment for Acne Scars."

Lasers in Surgery and Medicine, vol. 53, no. 5, pp. 610–615

10. Xu Y. and Deng. (2018): Ablative Fractional CO2 Laser for Facial Atrophic Acne Scars. Facial Plastic Surgery : FPS, 34(2), 205–219.
11. Joo J. and Surgery, (2021): "Application of Topical Timolol After CO2 Laser Resurfacing Expedites Healing." Dermatologic Surgery. Retrieved June 22, 2023,
12. Wei D. and Hamblin. (2021): A randomized, controlled, split-face study of topical timolol maleate 0.5% eye drops for the treatment of erythematotelangiectatic rosacea. Journal of Cosmetic Dermatology, 20(12), 3968–3973.
13. Khan M. and Boyce., (2017): "The Role of Topical Timolol in the Treatment of Infantile Hemangiomas: A Systematic Review and Meta-analysis." Acta Dermato-Venereologica, vol. 97, no. 10, pp. 1167–1171
14. Yosipovitch G. and Xiong. (1998): Time-dependent variations of the skin barrier function in humans: transepidermal water loss, stratum corneum hydration, skin surface pH, and skin temperature. The Journal of Investigative Dermatology, 110(1), 20–23.