Review Article

Timolol A Novel agent in Wound Healing: Clinical Advantages, Research Gaps and future Clinical Applications

Sarabjit Singh[1], Tarundeep Singh[2], Vivek Pahuja[3], Pankaj Dugg[4], Geeta Arora[5], Bhupinder Singh Walia[6], Girish Singla[7]

[1]Associate Professor, Department of Surgery, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India. [2]Associate Professor, Department of Medicine, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India. [3]Associate Professor, Department of Surgery, Dr. B. R. Ambedkar State Institute of Medical Science, SAS Nagar, Punjab, India. [4]Assistant Professor, Department of Surgery, Government Medical College, Amritsar, India. [5]Professor, Lovely Professional University, Punjab, India. [6]Associate Professor, Department of Surgery, Government Medical College, Amritsar, India. [7]Assistant Professor, Department of Surgery, Adesh Medical College & Hospital, Kurukshetra, Haryana, India

Abstract

Background: This review investigates the function of topical timolol in wound healing and its potential medical applications. Wound healing is a complex process, and novel approaches are currently being researched to improve it. Timolol, a nonselective beta-blocker used predominantly to treat glaucoma and hypertension, has demonstrated promise in promoting wound healing via multiple mechanisms. These mechanisms include the inhibition of beta-adrenergic receptors, the reduction of inflammation, the enhancement of angiogenesis, and the modulation of matrix metalloproteinases. According to studies, timolol accelerates re-epithelialization, increases angiogenesis and granulation tissue formation, and decreases scar formation. Timolol may also be used to treat hypertrophic lesions, pyogenic granulomas, and infantile hemangiomas. To optimize delivery regimens and assess long-term effects, however, further research, including large-scale clinical trials, is required. This review's findings indicate that topical timolol holds promise as a treatment option for wound healing and other medical conditions characterized by anomalous tissue growth.

Keywords: Timolol, wound healing, beta blockers.

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Introduction

People of advanced age are more likely to suffer from chronic ulcers. Worldwide, healthcare systems are overwhelmed by the impact of chronic wounds. In both outpatient and inpatient settings, the reported prevalence of chronic wounds among British citizens varies between 3.55 and 3.73 per 1000.[1] The reported point prevalence of chronic leg ulcers in an Australian community is 0.11%.[2] An annual expenditure of billions of dollars affects over 6 million people in the US alone. Most chronic wounds are caused by vascular insufficiency, neuropathy, or prolonged pressure. The others have a wide range of unusual causes.[2]

A wide variety of cells, including keratinocytes, fibroblasts, and others, must migrate and proliferate in perfect harmony for a cutaneous lesion to heal.[3] When damaged, cells move in a certain direction towards the wound bed's centre to start healing and re-establish epithelial integrity .In order to re-epithelialize, the epidermis triggers the dermal and epidermal cells to produce cytokines, growth factors, proteases, and extracellular matrix components, which in turn control the migration and proliferation of keratinocytes.[4] All three of the main cell types in skin—keratinocytes, fibroblasts, and melanocytes—express the b2-AR subtype of b-ARs on their membranes. The association between cutaneous disease and abnormalities in keratinocyte b2-AR activity or density is intriguing.[5,6] Wound healing can be accelerated by b2-Adrenergic receptor antagonists through many pathways, the most significant of which is enhanced keratinocyte migration. Scientific investigations and anecdotal evidence suggest that the nonselective b-blocker timolol facilitates wound re-epithelialization by inhibiting the epidermal autocrine b2-adrenergic receptor network. We looked at how topical timolol affected chronic ulcers in this study.

The purpose of this literature review is to investigate the possible medicinal applications and functions of topical timolol in wound healing.

Materials and Methods

Various electronic databases, including Google Scholar, MEDLINE, and PubMed are utilized to conduct a thorough literature search. The search included the keywords "topical timolol," "wound healing," "beta-blocker," and "medical treatments." Both in vitro and in vivo investigations published

Address for correspondence: Dr. Pankaj Dugg,
Assistant Professor, Department of Surgery, Government Medical College, Amritsar, India
E-mail: dr_dugg@hotmail.com

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from 2010 to 2024 were evaluated.

Literature review:

Surgical practice frequently involves the treatment of chronic wounds. Typically, they are characterized as ulcers that do not exhibit any symptoms of healing even after undergoing 6 weeks of therapy. While there are several causes, some typical ones are diabetic foot ulcers, venous ulcers, and pressure ulcers.[7] The incidence rate of chronic ulcers is around 1.51 per 1000 individuals in the community. The illness impacts 1% of the adult population and rises to 3.6% in those aged 65 and beyond.[8]

They usually remain resistant to conventional therapies thus not only affecting their quality of life but also pose a significant financial burden. Various new modalities have been developed but their availability, affordability, efficiency and complexity remain the issue of concern. Thus, a need for an agent which is cheap, easily available, efficient and easy to apply has always been felt.[9]

For keratinocytes and fibroblasts, among other cells, to migrate and proliferate in unison, the biological process of skin wound healing is intricate and strictly controlled.[10] When the skin is injured, it triggers the dermal and epidermal cells to create cytokines, growth factors, and proteases. These substances help in the formation of extracellular matrix components, which have a role in regulating the migration and proliferation of keratinocytes. Keratinocytes are necessary for the regeneration of the epidermis.[11] Following skin damage, cells undergo migration towards the central region of the wound bed to initiate the process of repair and re-establish the integrity of the epidermis. The injury-induced direct migration of keratinocytes is influenced by several variables, such as chemotaxis and contact-induced inhibition.[12] One of the main factors in wound healing is directed migration, which refers to the movement of cells toward the wound.[13,14] As evident from 2D and 3D studies, directed migration plays a critical role in wound recovery.[15] The b2-AR subtype is the sole subtype of b-ARs that is present on the membranes of the primary cell types found in the skin, namely keratinocytes, fibroblasts, and melanocytes. Abnormalities in either the functioning or density of keratinocyte b2-AR have been linked to skin diseases.[5,6,16] Studies have shown that beta 2-Adrenergic receptor antagonists enhance wound healing through many pathways, with the most significant being the enhancement of keratinocyte migration.

One such topical application is Topical Timolol, a nonselective beta-blocker traditionally used to treat glaucoma and hypertension, is one such area of investigation. Studies on Topical Timolol suggest that it can contribute positively towards wound healing by promoting cell proliferation and migration. Topical Timolol has been found to promote wound recovery by enabling keratinocyte migration into the wound, thereby facilitating re-epithelization.

Tang et al,[17] documented a case of a 43-year-old female patient who arrived with a persistent wound in the left mid-back region. The incision was 26 cm2 in area and had a depth of 3.5 cm. It was caused by a thoracotomy performed 15 months ago for open heart surgery, during which drainage tubes were put to remove secretions. Despite undergoing conservative therapies such as foam dressing, negative pressure wound therapy, and daily application of topical recombinant human platelet-derived growth factor for a duration of 3 weeks, there were no observed changes in the condition. As previous therapies did not produce the intended outcomes, the patient initiated a therapy regimen involving the application of timolol drops 0.5% on wounds treated with soft silicone. The patient administered three to four drops of the medication daily. Over the course of 8 weeks of therapy with timolol, the wound underwent full epithelialization without any significant problems.

A 67-year-old male patient with diabetes and chronic venous insufficiency presented with a chronic lesion measuring 4.2 cm2 on his left leg. Despite undergoing conventional therapy for 7 months, the wound failed to heal. The biopsy of the wound margins revealed alterations consistent with venous insufficiency and leukocytoclastic vasculitis. The patient had treatment with timolol eye drops at a concentration of 0.5%, administering three to four drops each day. Additionally, the patient took pentoxifylline pills at a dosage of 400 mg, three times a day. The patient administered the timolol drop in conjunction with cadexomer iodine gel to the wound and used Silva Sorb gel on alternate days. Indications of a modest amelioration became seen after a duration of 4 weeks. The patient subsequently ceased using pentoxifylline due to its adverse effects. Over the course of the following 83 days, the lesion exhibited significant improvement and finally achieved full epithelialization.[18]

Braun et al,[19] documented the case of an octogenarian lady with a medical background of venous insufficiency. The patient had previously undergone several treatments for various severe sores on both ankles, which were a result of recurrent injuries that occurred a year prior. Additionally, the patient had also undergone a surgical procedure on one of her thighs. Notwithstanding these interventions, the patient's wound remained at a size of 3.2 cm2 after a period of 6 months. The patient had treatment with timolol 0.5% eye drops, applying one drop per week for every 2 cm2 of the wound edge. This was followed by treating the wound with silicone foam and a three-layer compress. The patient's wounds fully healed within a span of 8 weeks. A 70-year-old lady, who has a medical history of venous insufficiency, osteoporosis, and beta thalassaemia, came to the clinic with a long-lasting wound on the back of her right leg that started 3 months ago. The patient's wound was managed with conventional dressings, but there was no notable enhancement observed. A weekly application of Timolol 0.5% drop was provided to the wound, at a rate of one drop per 2 cm2. Following this, the wound was wrapped with silicone foam and a four-layer compress. This treatment resulted in significant improvement of the 1 cm2 wound within a period of 7 weeks. A second female patient arrived with a 4.8 cm2 wound caused by an injury on the left side of her back. After receiving daily therapy with timolol 0.5% drops for a period of 8 weeks, she made a full recovery. A different female patient who had a lesion caused by pressure on the upper right thigh had daily treatment with timolol for a duration of 4 weeks. As a result, the size of her wound decreased from 2 to 0.6 cm2. A male patient suffering from sickle cell anaemia and venous insufficiency presented with a wound located above the left inner ankle. The patient had treatment with timolol drops on a weekly basis for a duration of

8 weeks. He saw a 21% enhancement in his condition and a decrease in wound size from 3.6 to 2.9 cm2.[19]

A 92-year-old lady, who has a medical history of ischaemic heart disease, has two chronic wounds on her left leg due to venous insufficiency. Despite undergoing normal treatments for 4 months, the wounds have not shown any improvement. To address this, the woman was administered timolol eye drop 0.5% on one of the wounds, with a dosage of four drops per day. Both wounds were treated with hydrocolloid film and silicone foam dressings and had an initial size of approximately 20 cm2. Following a duration of 6 weeks, the use of topical timolol resulted in a reduction of 8 cm2 in the size of the wound. Following a duration of 12 weeks, the healing process reached full completion. There were no identified problems associated with the administration of timolol.[20]

A 76-year-old male patient appeared with a 10 x 11 cm incision in the scalp area resulting from the removal of squamous cell carcinoma during Mohs surgery. Following three years of utilising conventional therapies, a little amount of vascular granulation tissue formed at the site of his incision. The patient received topical timolol, administered as three to four drops twice a day. The dosage was then lowered to once daily owing to stimulation, and further decreased to every other day, and eventually to every 2 to 3 days. After a period of 4 months, the granulation tissue was flattened, and the wound was completely covered by epithelial cells.[21]

Two infants, both aged 1 year, were diagnosed with generalized junctional epidermolysis bullosa. They experienced ongoing nail bed and neck skin fold lesions, despite the topical use of corticosteroids and silicone dressing for a period exceeding 2 months. 0.5% of Timolol eye drops 0.5% were used to treat nail wounds. Two drops were applied twice daily for 3 weeks. For the neck wounds, three drops were used twice daily for 8 weeks. As a result, the nail wounds showed complete healing (100%), while the neck wounds exhibited an 80% improvement. The patients did not experience any issues.[22]

The topical use of timolol has been found to enhance wound healing in individuals with persistent diabetes and venous insufficiency. Research was conducted on a total of 60 patients, divided into two groups of 30 each, who received treatment for chronic leg wounds caused by diabetes and venous insufficiency. One cohort was administered topical timolol 0.5% in addition to the normal medication, whereas the other cohort was just subjected to the standard treatment. The wounds of the patients receiving timolol showed a 25% improvement at week 4, a 44% improvement at week 8, and a 65% improvement at week 12. In comparison, the control group only showed a 12% improvement at week 4, a 22% improvement at week 8, and a 30% improvement at week 12. These results suggest that the use of topical timolol led to faster healing of the wounds.[3]

The impact of applying topical timolol on the wound healing process of a vasculitis wound was documented in a 40-year-old male patient with no pre-existing medical conditions. The patient sought medical attention due to a lesion measuring 5 cm in diameter on the lower left extremities. The wound had developed three weeks prior and vasculitis was detected in the wound biopsy. The patient received systemic prednisolone at a daily dose of 60 mg for a duration of 1 month. Subsequently, dapsone was co-administered at a daily dose of 50 mg. Unfortunately, no improvement was noted. The patient was prescribed Timolol eye drop 0.5% to be administered five drops three times a day, targeting both the centre and margins of the incision. The wound exhibited substantial improvement throughout the weekly follow-up sessions and fully healed after a duration of 6 weeks.[23]

Rai et al,[24] did a randomized controlled experiment to examine the effectiveness of topical timolol with saline in treating chronic venous ulcers. One cohort received a single drop of 0.5% topical timolol every other day for a duration of 4 weeks. Weekly measurements of ulcer edges were taken, and the extent of the ulcer was determined during a period of four weeks. Patients were subjected to identical dressing and measuring procedures using saline solution for a duration of 4 weeks. The healing rate was evaluated by calculating the percentage of reduction in ulcer area for both groups after 4 weeks. The study demonstrated that individuals in the timolol group saw a substantial decrease in ulcer size (86.80%) compared to the saline group (43.82%) after 4 weeks of therapy.

Menezes et al,[25] did cross-sectional research to assess the effectiveness of topical timolol in treating chronic non-healing foot ulcers. There was a total of 95 patients. Timolol was administered at a precise dosage determined by the size of the ulcer (3 drops per square centimeters per day, which is equivalent to 0.25 milligrams per square centimetre per day). The application of Timolol occurred on days 1, 3, and 7.A desiccated bandage was administered. Patients were monitored on day 15 and day 30. On each occasion, the ulcer was evaluated, and its dimensions were recorded. A statistically significant decrease (p=0.001) in the average proportion of ulcer area was seen on day 15 and day 30.

Results

Table 1: Past studies showing outcome of Timolol use in wound dressings

Study year	Design	Number of patients	Site of lesion	Intervention	Dose	Duration	Treatment	outcome
Tang JC,2012,[17]	Chronic wound/CR	1	Mid-back wound	Timolol 0.5% drops soft silicone dressing	3-4 drops daily	8 weeks	Foam dressing, negative pressure, and three weeks of topical recombinant human platelet-derived growth factor application for 3 weeks	Epithelialized completely

Lev-Tov H,2013,[18]	Chronic wound/CR	1	Calf	Timolol eye drop 0.5% 400 mg pentoxifylline tablets	3 to 4 drops daily thrice daily	3 months	Compression, weekly debridement, collagenase ointment, and daily iodine gel per seven months	Completely epithelialize
Braun LR,2013,[19]	Chronic wound/CR	1	Ankles	Timolol eye drop 0.5% silicone foam three-layer compress	1 drop weekly per 2 cm2	8 weeks	Foam dressing, bilayered live skin comparable, porcine small intestine, compression bandages, graft/6 months	Completely healed
Braun LR,2013,[19]	Chronic wound/CR	1	Back of leg	Timolol 0.5% drop silicone foam four-layer compress	1 drop weekly per 2 cm2	7 weeks	Two compression bandages, a skin equivalent. and foam dressings,	Improved the 1 cm2 wound
Manahan MN, 2014,[20]	Chronic wound/CR	1	Leg	Timolol 0.5% drops dressed with hydrocolloid film and silicone foam	4 drops daily	12 weeks	Ultrasonic wound debridement, antibiotics, alginate and foam dressings for four months.	Healed completely
Beroukhim K,2014,[21]	Chronic wound/CR	1	Scalp	Timolol 0.5%	3-4 drops twice daily	4 months	Conventional therapies lasting for a duration of three years	Fully epithelialized
Chiaverini C, 2016,[22]	Chronic wound/CS	2	Nail bed, Neck skin fold	Timolol 0.5%, closed dressing	2 drops twice daily/nail. 3 drops twice daily/neck	3 weeks/nail 8 weeks/ neck	Silicone dressing and topical corticosteroids/ two months	100% improvement for the nail, 80% for the neck
Thomas B, 2017,[3]	Chronic wound/RCT	30	Lower extremity	Timolol 0.5%, Standard therapy	1 drop for every 2 cm of wound daily	12 weeks	Conventional treatment includes the use of antibiotics, debridement absorbent dressing and strict blood sugar control	The improvement was twice that of the control group
Alsaad AMS, 2019,[23]	Vasculitis wound/CR	1	Lower limbs	Timolol 0.5%	5 drops thrice daily	6 weeks	Dapsone and Systemic prednisolone/3 weeks	Healed completely
Rai, A. K,2020,[24]	Chronic Venous Ulcers/RCT	10	Lower limb	Timolol 0.5%	one drop was instilled every 2 cm^2 of wound edge alternate day	4 Weeks	saline dressing	Overall mean reduction in the ulcer area was twice the patients with timolol dressing as compared to the patients treated with saline dressing. There was a complete closure of the ulcer in five patients
Menezes, J. V, 2024,[25]	Chronic foot ulcers/ cross sectional study	95	Foot	Timolol 0.5%	3drops/cm2/day on day 1,3,7	30 days	Standard treatment	Significant reduction in area on day 15 and 30

Discussion

Wound healing is a complex process involving a series of interconnected events designed to restore the integrity and function of wounded tissues. Existing wound-healing treatments are diverse, but there is a growing interest in investigating novel approaches.

Different mechanism has been suggested by different studies

which emphasis the significant role of the timolol in wound healing that can be defined as follows:

a) Angiogenesis and Granulation Tissue Formation: One of the main mechanisms is the blockade of beta-adrenergic receptors, which results in a decreased inflammatory response and enhanced angiogenesis. Timolol also modulates the activity of matrix metalloproteinases, thereby fostering the synthesis and remodeling of extracellular matrix components required for wound healing. Angiogenesis, the formation of new blood vessels, is essential to the healing process. It has been demonstrated that topical timolol enhances angiogenesis by promoting the expression of vascular endothelial growth factor (VEGF) and increasing endothelial cell proliferation. Additionally, it has been discovered that timolol stimulates the formation of granulation tissue, the collagen-rich tissue that occupies the wound bed. These effects contribute to accelerated wound healing.[26,27]

b) Enhanced Re-epithelialization: Numerous studies have shown that topical timolol can enhance re-epithelialization, the process in which epithelial cells migrate and cover the wound site. In a mouse model, Smith et al, found that wounds treated with timolol experienced accelerated re-epithelialization compared to wounds treated with a placebo. The application of topical timolol to patients with chronic wounds improved re-epithelialization, according to clinical investigations. Dressing with foam, negative pressure and daily topical recombinant human platelet-derived growth factor/3 weeks.[28,29]

c) Scar Reduction and Potential Medical Application: The benefits of topical timolol extend beyond traditional wound recovery. In wound healing, excessive fibrosis is a common concern. There is evidence that topical timolol can reduce scar formation and improve cosmetic outcomes. Emerging evidence suggests its efficacy in a variety of medical treatments. Timolol has shown promise in treating hypertrophic scars, pyogenic granulomas, and infantile hemangiomas, among other conditions. Due to its anti-inflammatory and anti-angiogenic properties, it could be used to treat these conditions.[30-34]

Research gaps in this area

The existing literature on the role of topical timolol in wound healing includes clinical trials, systematic reviews, prospective studies, and in vitro experiments conducted in a variety of settings. These studies investigated the efficacy of topical timolol on a variety of wound types, such as diabetic foot ulcers, hypertrophic scars, burn wounds, infantile hemangiomas, pyoderma gangrenosum, and surgical wounds. The findings indicate that topical timolol has the potential to promote wound healing, reduce scar formation, and enhance cosmetic outcomes.

Despite the existing research, significant research gaps remain in this field:

Standardized Protocols: The optimal administration regimens for topical timolol are presently unknown. It is difficult to establish standardized protocols due to variations in concentration, frequency, and duration of application across studies. A lack of consensus regarding the safest and most effective dosage range impedes clinical implementation.

Safety Profile: While topical timolol is generally well-tolerated, additional research is required to assess its safety profile comprehensively, particularly in vulnerable populations such as infants, pregnant women, and patients with comorbidities. To evaluate possible adverse effects and systemic absorption hazards, long-term follow-up studies are necessary.

Large-scale Clinical Trials: Most studies conducted to date have been of a limited scope and generalizability. To provide robust evidence on the efficacy, tolerability, and long-term outcomes of topical timolol, large-scale randomized controlled trials with diverse patient populations are required. These studies would aid in validating previous findings and guiding clinical practice.

Comparative Studies: There are a limited number of head-to-head studies comparing topical timolol to other standard wound healing treatments. Comparative efficacy research can assist in determining the relative advantages and disadvantages of topical timolol in comparison to existing interventions, allowing clinicians to make more informed treatment decisions.

Mechanistic Understanding: While some studies have investigated the mechanisms by which topical timolol promotes wound healing, additional research is required to elucidate the precise molecular pathways involved. A deeper comprehension of the underlying mechanisms can guide the development of targeted therapies and increase the therapeutic potential of timolol in wound healing.

Analysis of cost-effectiveness: The economic ramifications of incorporating topical timolol into wound care protocols have not been examined in depth. Analyses of cost-effectiveness would aid in determining the financial viability and prospective impact on healthcare systems.

Addressing these research deficiencies will contribute to a more complete understanding of the role of topical timolol in wound healing and facilitate its integration into clinical practice in a manner that is effective and supported by evidence. Future research should concentrate on standardizing protocols, evaluating safety profiles, conducting large-scale trials, conducting comparative efficacy research, examining underlying mechanisms, and evaluating cost-effectiveness.

Conclusion

The literature review emphasizes the potential function of topical timolol in wound healing and its medical applications. The results indicate that timolol can enhance re-epithelialization, promote angiogenesis and granulation tissue formation, and decrease scar formation. In addition to wound healing, its application extends to numerous medical conditions characterized by abnormal tissue growth. To establish optimal administration regimens, evaluate long-term effects, and investigate the full potential of topical timolol in medical treatments however, additional research, including large-scale clinical trials, is required.

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Conflicts of interest

There are no conflicts of interest.

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