

## A COMPARITIVE STUDY BETWEEN EFFICACY OF TOPICAL TIMOLOL DRESSING VERSES POVIDONE IODINE DRESSING IN NON-HEALING ULCER

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### ABSTRACT

**Background:** Chronic wounds are those that fail to heal in an orderly and timely manner, often due to inflammation, hypoxia, and poor cellular response.  $\beta$ -2 adrenergic receptor (B2-AR) activation impairs keratinocyte migration, a crucial factor in wound healing. Topical  $\beta$ -blockers like timolol can block B2-AR, promoting keratinocyte and fibroblast migration, angiogenesis, and epithelialization. **Aim:** To compare the efficacy of topical timolol versus povidone-iodine dressings in non-healing ulcers by evaluating the mean reduction in ulcer area over 4 weeks. **Material and Methods:** A randomized controlled study on 50 patients with Wagner grade I–II lower extremity ulcers. Patients were assigned to two groups: Group A: 25 patients treated with topical 0.5% timolol (3 drops/cm<sup>2</sup> every alternate day) Group B: 25 patients treated with povidone-iodine dressing. Ulcer dimensions and other clinical parameters were recorded on Day 1, 15, and 30. **Result:** Ulcer Area Reduction (Day 30): Group A: 18.5 cm<sup>2</sup>  $\rightarrow$  significant ( $p < 0.00007$ ); Group B: 19.2 cm<sup>2</sup> ( $p < 0.39$ ). Mean Area Reduction: At Day 15: Group A – 4.58 cm<sup>2</sup> vs Group B – 2.33 cm<sup>2</sup> ( $p < 0.00001$ ). At Day 30: Group A – 4.23 cm<sup>2</sup> vs Group B – 0.47 cm<sup>2</sup> ( $p < 0.00001$ ). Wound Grade: More patients with Grade II ulcers showed better improvement in Group A. No systemic side effects of timolol observed. No significant differences in haemoglobin, albumin, WBC count, or HbA1C between groups. **Conclusion:** Topical timolol is a cost-effective, safe, and significantly more effective alternative to povidone-iodine for healing chronic ulcers (Wagner Grade I–II). It shortens healing time and can reduce the burden of chronic dressings without systemic complications.

## INTRODUCTION

Chronic wounds are defined as, wounds that fail to proceed in the orderly process of healing and producing an unsatisfactory anatomical functional integrity. Chronicity of wounds is perpetuated by repeated trauma, hypoxia, poor perfusion and excessive inflammation. Unresponsiveness to normal regulatory stimulus of wound healing leading to failure of normal growth factor synthesis. In chronic wounds, it has been found that there is increased break down of growth factors with over expression of proteolytic activity and failure of normal anti-protease inhibitor mechanisms. There is presence of senescent fibroblasts with poor proliferative potential and decreased growth factor receptor expression in chronic wounds.

$\beta$ -2 adrenergic receptor (B2-AR) is expressed primarily on human keratinocytes. Non healing is

possibly because of chronic activation of  $\beta$ -2 adrenergic receptor in the keratinocytes by endogenously generated catecholamines, which inhibits keratinocyte migration. Keratinocyte migration is a key component in wound healing and it is required for skin re-epithelization and complete wound repair.

Blocking of B2-AR using  $\beta$ -blockers has been reported to promote wound healing through

- keratinocyte migration,
- promotion of angiogenesis,
- increased dermal fibroblast migration
- epidermal differentiation.

Topical timolol, a B2-AR antagonist, is used to promote wound healing, a commercially available B2-AR antagonist, used as an intraocular glaucoma medication has been shown to promote wound healing when instilled in chronic leg ulcers. The purpose of this study was to assess the efficacy of

topical timolol in wound healing. B2-AR is the dominant subtype expressed on keratinocyte surfaces. Keratinocyte migration occurs by the facilitation of chemotaxis, the polarization of cells, and activation of extracellular signal-related kinases essential in the signalling of promigratory pathways. The B2-AR activation inhibits keratinocyte migration by activating the serine/threonine phosphatase 2A, which downregulates phosphorylation of extracellular signal-related kinases necessary for migration. Therefore, B2-AR antagonists prevent the phosphorylation of phosphatase and downstream extracellular signal-related kinase promotion, inducing a promigratory pathway in keratinocytes. The B2-AR antagonists improve the ability of keratinocytes to respond to such migratory signals, whereas the B2-AR agonists decrease keratinocytes ability to respond. Angiogenesis and dermal fibroblast proliferation are also regulated by B2-ARwounds

**Aim:** To compare the efficacy of Topical Timolol dressing versus Povidone Iodine dressing in an Ulcer. To compare the mean reduction in ulcer area at the end of 4 weeks

1. To analyse the efficacy of Topical Timolol dressing overtime in patients with nonhealing ulcers.
2. To compare its efficacy over conventional dressing of a non-healing ulcer.
3. To study other variable factors which may play a role in wound healing.

## MATERIALS AND METHODS

The study population contains 50 patients admitted with lower extremity ulcers meeting the inclusion and exclusion criteria within 2 yrs. study period with purposive sampling technique.

A complete detailed history, physical evaluation, relevant blood investigations, radiological investigations will be done and correlated with Wagner's grade I-II and patients will be grouped accordingly. Each patient after randomization will be allotted into treatment or control group.

- Group A (treatment group). 25 patients with ulcer receiving Topical Timolol (3drops of 0.5% Timolol/cm<sup>2</sup> area on alternate days)
- Group B (control group). 25 patients with povidone-iodine dressing.

The improvement will also be evaluated with photography and the ulcer reduction rate in both groups will be calculated at the end of 15days and 1 month after beginning the treatment.

## RESULTS

Among 50 patients assessed, 25 patients in group A (Timolol treated) and 25 patients in group B (povidone iodine treated) Distribution based on Wagner's Grade of Ulcer : 24% in group A and 40% in group B patients had Wagner's grade 1 ulcer. 76%

in group A and 60% in group B patients had Wagner's grade II ulcer. **Mean length of the ulcer:** In Group A Mean length of ulcer on day 1,15 & 30 is 6.2cm, 5.92cm, 5.44cm respectively with P Value of <0.04 whereas in Group B the mean length is 5.9cm, 5.44cm, 5.70cm respectively with P Value of <0.33. **Mean breadth of the ulcer:** In Group A Mean breadth of ulcer on day 1,15 & 30 is 4.48cm, 3.85cm, 3.42cm respectively with P Value of <0.02 whereas in Group B the mean breadth is 3.66cm,3.52cm, 3.29cm respectively with P Value of <0.36. **Mean area of Ulcer:** In Group A Mean area of ulcer on day 1,15 & 30 is 27.3cm, 22.8cm, 18.5cm respectively with P Value of <0.00007 whereas in Group B the mean area is 21.97cm, 19.6cm, 19.2cm respectively with P Value of <0.39. **On Comparison of mean (SD) Reduction in area at Day 15:** In Group A 4.58cm<sup>2</sup> and in Group B 2.33cm<sup>2</sup> with P Value of <0.00001. **On Comparison of mean (SD) Reduction in area at Day 30:** In Group A 4.23cm<sup>2</sup> and in Group B 0.47cm<sup>2</sup> with P Value of <0.00001. **Comparison of mean (SD) Haemoglobin:** In Group A haemoglobin is 13.28 and in Group B haemoglobin is 12.78. **Comparison of mean (SD) total WBC count:** In Group A count is 7012 and in Group B count is 7284. **Comparison of mean (SD) Albumin:** Group A 3.94 and Group B 3.72 with P Value of <0.5. **Comparison of mean (SD) HbA1C at Day 1:** Group A 6.64 and Group B 6.85 with P Value of <0.16. **Comparison based on Doppler findings:** Shows abnormal doppler findings in 16 patients from Group A and 10 patients from Group B. Normal doppler findings in 9 cases from Group A and 15 cases from Group B with P Value of < 0.08.

## DISCUSSION



Day 1 of Ulcer treated with Topical Timolol



#### Day 30 of Ulcer treated with Topical Timolol

Total 50 patients were included in the study from March 2022 till June 2024. Patients were randomly selected into two groups i.e., Group-A and Group-B. Each group has 25 patients. Out of 25 patients in Group-A -mean age was 49.92 years, 13 of them were aged below 50 years and 12 people were aged more than 50 years. Out of 25 in Group-B- mean age was 51.08 years, 12 people were aged below 50 years and 13 people were aged above 50 years. Out of 25 patients in the Group-A -10 were female and 15 were male. Out of 25 patients in the Group-B - 9 were female and 16 were male. So total 19 females and 31 males were included in the study.

Most common involved limb was right lower limb i.e., 27 patients in total study group. Out of 25 patients in the Group-A -14 people had ulcer in right limb and 11 people in left limb. Out of 25 patients in the Group-B- 13 people in the right limb and 12 people had ulcers in the left limb Most of the ulcers were grade 2 in both groups i.e., 19 in Group-A & 15 in Group-B. Out of 25 patients in the Group-A -6 people were classified into grade 1 ulcer and 19 into grade 2. Out of 25 in Group-B 10 were classified as grade 1 and 15 were classified into grade 2.

In Group-A: Mean length of ulcer on day 1 was 6.2 cm, breadth was 4.48 cm and area was 27.3cm<sup>2</sup>. On day 15 mean length was 5.92 cm, breadth was 3.85 cm and area was 22.8 cm<sup>2</sup>. Reduction in area was 4.58 cm<sup>2</sup>. Mean length on day 30 was 5.44 cm, breadth was 3.42 cm and area were 18.5 cm<sup>2</sup>.Reduction in area at day 30 was 4.23 cm<sup>2</sup>.

In Group-B: Mean length of ulcer on day 1 was 5.9 cm, breadth was 3.66 cm and area was 21.97 cm<sup>2</sup>. Mean length of ulcer on day 15 was 5.44 cm, breadth was 3.52 cm and area was 19.6 cm<sup>2</sup>. Reduction in area was 2.33 cm<sup>2</sup> which was statistically significant with a P value of <0.00001.

Mean length on day 30 was 5.7 cm, breadth was 3.29 cm and area were 19.2 cm<sup>2</sup>. Mean reduction in area at day 30 was 0.47 cm<sup>2</sup>. which was statistically significant with a P value of <0.00001.

Mean haemoglobin in Group-A was 13.28 gm% whereas in Group- B it was 12.78 gm%. Mean total WBC count was 7012 cells/mm<sup>3</sup> in Group-A whereas 7284 cells/mm<sup>3</sup> in Group-B. This result was comparable and statistically not significant with a P value of 0.50.

Mean albumin was 3.94 in Group-A whereas 3.72 in Group-B. This result was comparable and statistically not significant with a P value of 0.5.

Mean HbA1c in Group-A it was 6.64 whereas it was 6.85 in the Group-B. This result was comparable and statistically not significant with a P value of 0.16.

Out of 25 patients in Group-A; 9 people had normal doppler report and 16 people had abnormal report. Out of 25 patients in the Group- B; 15 people had normal report and rest 10 had abnormal findings on the doppler of involved limb. This result was comparable and statistically not significant with a P value of 0.08.

- 1) In 2016 a study done by Michelangelo MD; Filoni, Angela MD; Domenico MD, Paolo MD; Giudice MD on action of 0.5% topical timolol on chronic refractory wounds showed that a statistical significant improvement in % of area reduction (up to 98.75%) without any systemic side effects
- 2) In 2020 a randomized controlled trial done by Abhay K rai, K Janani, and Reena rai on efficacy of topical timolol versus saline in chronic venous ulcer showed that the mean reduction in the ulcer size in timolol group was 86.80%, and in saline group 43.82% at the end of 4 weeks. Thus topical timolol is an easy, non-invasive therapy that can be recommended for chronic ulcer.
- 3) A Study done on dec 2013 by Liza R.Braun,<sup>[16]</sup> on topical timolol for recalcitrant wounds showed that the mean reduction of wound size after 7 weeks of treatment was 78.2%.
- 4) Topical timolol promotes healing of chronic leg ulcer a study done by Bindhiya Thomas et al. J Vasc Surg Venous Lymph at Disord.<sup>[18]</sup> 2017 Nov. This is the first case-control study to assess the effect of topical timolol on healing of chronic venous and chronic diabetic ulcers. The mean percentage change in area at 4, 8, and 12 weeks was 25.29, 43.77, and 61.79 in the study group (treated with 0.5% topical timolol) and 11.92, 22.40, and 29.62 in the control group (treated with antibiotics and saline dressings). At end of 30 days the mean reduction in the area of an ulcer in timolol group was 4.23 cm<sup>2</sup> whereas control group was 0.47 cm<sup>2</sup> which was statistically significant.

## CONCLUSION

In our study to evaluate the efficacy of Topical Timolol dressing in healing of chronic foot ulcers, we conclude that it is effective in healing of ulcer - Wagner's grade 1 and 2 compared to Povidone-iodine dressings. There is statistically significant decrease in mean area of the ulcer at end of day 30. Topical Timolol application could bring down chronicity of dressing in the patients. It did not have any systemic complications. It is cost effective. With effective Haemoglobin, Albumin, controlled

glycaemic index, WBC counts, with appropriate antibiotics and well-motivated patient, topical Timolol seems to be fair alternative compared to other pharmacological applicants which costs much for the patient

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