

# Local Application of *Timolol* 0.5% Solution in Treating Chronic Non-Healing Ulcers – A Prospective Study

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## Abstract

Chronic non-healing ulcers are a variety of ulcers that occur mainly over the lower limb and are resistant to conventional therapy. There are modern treatments like various types of dressings and topical preparations available in the market. However, they are costly and may not be freely available to the general population. Topical usage of  $\beta_2$ -AR antagonists like timolol may promote wound healing by enabling keratinocyte migration into the wound to initiate the re-epithelisation. The objective of this study is to assess the effectiveness of topical timolol 0.5% in accelerating the wound healing process by observing the signs of healing. It is a prospective observational study conducted in Government General Hospital, Rangaya Medical College, Kakinada, after getting Institutional Ethical Committee approval from March 2021 to March 2023. One hundred patients with Chronic non-healing foot ulcers were taken for this study. Mean age was 47.64.60% of the study population was in the 20-55 years age group. Reduction in mean ulcer area was on day 15 and day 30 with topical application of timolol.

**Keywords:** Beta-Adrenergic Receptor antagonist; Chronic Non-Healing Ulcer; Mechanical debridement

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## INTRODUCTION

Chronic non-healing ulcers are those that do not respond to a regular way of conventional management, and they are resistant to healing even after 6 weeks.<sup>1</sup> They have multifactorial etiology and cause severe complications if not treated wisely. The prevalence is estimated to be about 1.51 per 1000 population.<sup>1</sup> It is seen in 1% of the adult population. 3.6% is noticed in those above 65 years.<sup>2</sup> It causes deterioration in quality of life, becomes a financial burden to the person's family, and even damages the healthcare system.

We have various types of treatment that include local application of dressings, debridement, and offloading. However, in some chronic non-healing ulcer cases, any of these modalities of treatment are not satisfactory. We desperately need a drug that is easily available, cost-effective, and easy to apply, easy for people to understand. Some studies found that local application of 0.5% timolol fulfills those desires.

Timolo is a Beta2 receptor antagonist. It is useful in the treatment of raised blood pressure, congestive cardiac failure, and

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ocular conditions like glaucoma and migraine.<sup>3</sup> Beta2 adrenergic receptors are present in keratinocytes. A topical application of Timolol acts by mobilizing the keratinocytes into the wound area and further by re-epithelisation.<sup>4,5</sup>

The objective of this study is to assess the safety of the patient after this local application, any adverse effects or drug interactions. The efficacy of topical application of 0.5% timolol solution is assessed by regular examination of the wound and by measuring the wound size at 15 and 30 days. Any decrease in size is to be recorded.

## METHOD

This study was conducted in Government General Hospital, Rangaraya Medical College, Kakinada, after getting Institutional Ethical Committee approval from March 2021 to March 2023. One hundred patients were taken for this study.

### Inclusion Criteria

More than 18 years age group, non-healing ulcers for more than 6 weeks with no progress were noticed even after 4 weeks of continuous treatment, size of 5 to 50 cm<sup>2</sup> and with granulation tissue. If more number of ulcers are present, the greatest is to be chosen. Bacteriologically sterile wound, the ulcer area must contain granulation tissue of nearly 50 percent.

### Exclusion Criteria

The exclusion criteria in this study are ischaemic limb ulcers, slough and debris wounds, wounds with dead bone and tendon, glaucoma patients, patients sensitive to beta blockers, chronic lung diseases, ischaemic heart diseases, and thyroid disorders.

After taking informed consent, some important details were noted in the record. They are age, sex, occupation, address, and socio-economic status, including chief complaints and duration, history of present illness, family history, personal history, and treatment history. Local examination findings like ulcer site, size, number, shape, margin, edge, floor, base, discharge, and surrounding area were noted. Discharge was to be sent for bacteriological examination. Specific drug treatment had to be given. Ulcer size was to be measured and plotted on graph paper. The size of the ulcer was recorded on the 1st day, 15th day and 30th day. Detailed clinical examinations for all peripheral pulses, cardiovascular system, and nervous system were conducted. Routine blood investigations and x-rays of the affected part were taken.

Drug administration method: The First ulcer was to be treated with various types of available treatments like debridement and dressings. Once bacteriological examination came as a sterile report and the ulcer area was filled with granulation tissue for more than 50%, the size of the ulcer had to be noted. Now, we had to apply timolol 0.5% solution locally and cover the area with dry dressings with a dosage of 3 drops/cm<sup>2</sup>/day = 0.25mg/cm<sup>2</sup>/day. These drops were to be applied on the 1st, 3rd and 7th days. The healing and size of the ulcer were assessed on the 15th and 30th day. All the data was to be recorded.

## RESULTS AND DISCUSSION

This study showed that the majority of ulcers are located over the plantar aspects of the foot in the pressure-bearing areas.

*Timolol efficiency assessment:* The ulcer area of day 1 was reduced to minimum size on day 15 and day 30. Table 1 and 2 shows

a significant reduction in ulcer area. A decrease in ulcer area on day 15 and day 30 was noted. The effect of timolol on the 20-50 years age group and the age group is similar.

*Age:* The youngest was 20 years old, and the oldest was 85 years old. The mean age was 47. 64.60% of them were in 20-55 years of age.

**Table 1.** Age and Frequency

Age Category	Frequency	Percentage (%)
20-29 years old	4	4 %
30-39 years old	6	6 %
40-49 years old	34	34 %
50-59 years old	20	20 %
60-69 years old	14	14 %
70-79 years old	16	16 %
80-89 years old	6	6 %

*Sex:* The male dominated by 60% while the female was 40%.

**Table 2.** Sex distribution

Age Category	Male	Percentage (%)	Female	Percentage (%)
20-29 years old	2	2.0	2	2.0
30-39 years old	10	10.0	3	3.0
40-49 years old	20	20.0	14	14.0
50-59 years old	12	12.0	11	11.0
60-69 years old	6	6.0	4	4.0
70-79 years old	4	4.0	3	3.0
80-89 years old	6	6.0	3	3.0
Total	60	60.0	40	40.0

*Occupation:* Most of the patients are agricultural laborers and manual workers.

**Table 3.** Occupation of the Patients

Age category	Agricultural and Manual Labourers	Others
20-29 years old	3	0
30-39 years old	6	0
40-49 years old	31	8
50-59 years old	21	6
60-69 years old	11	4
70-79 years old	8	1
80-89 years old	1	0
Total	81	19

Most of them are from low socio-economic groups and manual laborers.

*Ulcer duration:* > 6 weeks; 26.1% are of 12-16 weeks duration.

**Table 4.** Ulcer area on days 1, 15 and 30

Days	Number of patients	Minimum area (cm <sup>2</sup> )	Maximum area (cm <sup>2</sup> )	Mean (cm <sup>2</sup> )	SD	P value
Day 1	100	5 - 49	350 - 399	70..95	77.05	
Day 15	100	1 - 9	300 -349	51..88	64.86	0..001*
Day 30	80	1 - 9	250 - 299	39.95	54	

**Table 5.** Percentage of reduction in size of ulcer at days 15 and 30

	Number of patients	Min	Max	Mean	SD	Mean difference	P value
% of ulcer area reduction on day 15	100	8	69	37.6	152	-32	0.001*
% of ulcer area reduction on day 30	100	21	99	66..2	23		

Giving topical timolol for treating chronic non-healing ulcers is well understood. Kaur et al. demonstrated that timolol was useful in chronic diabetic foot ulcers.<sup>6</sup> Braun et al. and Vestita et al. showed the efficacy of timolol in treating chronic resistant wounds.<sup>7</sup> Similarly, there are cases reported where chronic ulcers were successfully treated with topical timolol.<sup>8</sup> In this study, we used timolol eye drops, commercially available as a 5 ml solution of 0.5% w/v timolol maleate. Oliver et al. said that the etiology in the case of diabetic ulcers are lack of blood sugar control, deformities, ill-fitting footwear, peripheral neuropathy, hypoperfusion, and dry skin.<sup>9</sup> Vestita et al also demonstrated the advantage of using topical in managing chronic non-healing ulcers.<sup>10</sup> Manhan et al. reported that they successfully treated chronic non-healing ulcers with topical timolol.<sup>11</sup> Similarly, many studies supported the application of topical timolol while treating chronic non-healing ulcers.<sup>12-14</sup> Larsen L et al also discovered a significant reduction in the size of ulcers after topical timolol administration.<sup>15</sup> Dabiri G. et al also determined that there is improved

cosmosis in surgical wounds with Timolol.<sup>16</sup>

Al Mokadem SM et al. found significant improvement in the prognosis of acne with topical timolol application.<sup>17</sup> Alcántara-Reifs CM et al also published an advantage of topical timolol in managing Kaposi sarcoma.<sup>18</sup> Chiaverini C et al found a good response in chronic wounds of junctional epidermolysis bullosa with topical timolol.<sup>19</sup> Yoon DJ et al expressed that topical timolol may be safe and effective in various dermatological conditions.<sup>20</sup> Chen L et al. demonstrated topical timolol in infantile haemangioma and other skin conditions.<sup>21</sup> Baltazard T et al evaluated and supported the safety and benefits of using timolol locally in chronic non-healing venous ulcers.<sup>22</sup> Cahn BA et al. found that topical timolol is safe and effective in healing recalcitrant wounds of various etiologies.<sup>23</sup> However, there is no need for any special training, and it could be done even in rural areas. There were no adverse drug reactions or drug interactions seen in our study.

## CONCLUSION

Managing chronic non-healing ulcers is complicated. Each method of treatment had its drawbacks and limitations. In this study, topical application of timolol was effective in treating Chronic non-healing ulcers. Other studies also supported the findings. In India, with a large population residing in rural areas, timolol is available at cheaper rates. It also does not require any special expertise in its application, making it a good solution at the primary healthcare level.

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