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SHORT-CONTACT TOPICAL RETINOIC ACID OINTMENT IN CHRONIC NON-HEALING WOUNDS: A RANDOMIZED CONTROLLED TRIAL FROM A TERTIARY CARE CENTRE

Surgery

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ABSTRACT

Background: Chronic non-healing wounds remain a major therapeutic challenge because of prolonged inflammation, impaired angiogenesis, extracellular matrix degradation, and delayed epithelialization. Retinoic acid has demonstrated biologically active effects on fibroblast proliferation, collagen synthesis, epithelial differentiation, and inflammatory modulation. **Aim:** To evaluate the efficacy of short-contact topical 0.05% retinoic acid ointment in chronic non-healing wounds compared with conventional saline dressings.**Methods:** A prospective randomized controlled trial involving 50 patients with chronic non-healing ulcers was conducted at a tertiary care teaching hospital. Patients were randomized into intervention and control groups. The intervention group received short-contact topical retinoic acid ointment, while the control group underwent conventional saline dressings. Serial wound dimensions including area and depth were assessed over four weeks. **Results:** The intervention cohort demonstrated significantly greater reduction in wound surface area and wound depth compared with controls. Accelerated granulation tissue formation and earlier achievement of ≥50% wound reduction were observed in retinoic acid-treated wounds. No significant local hypersensitivity or systemic adverse effects were documented. **Conclusion:** Short-contact topical retinoic acid appears to be a safe, inexpensive, and clinically effective adjunctive therapy in chronic wound management and may improve proliferative-phase healing dynamics in chronic ulcers.

KEYWORDS

INTRODUCTION

Chronic non-healing wounds constitute a substantial burden in surgical practice because of prolonged morbidity, recurrent infection, repeated hospitalization, and increased healthcare expenditure. Chronic wounds are characterized by failure to progress through the normal phases of wound healing and frequently remain arrested within a persistent inflammatory state. Diabetes mellitus, peripheral vascular disease, venous insufficiency, neuropathy, pressure-related ischemia, malnutrition, and smoking significantly contribute to delayed tissue repair.

Physiological wound healing involves a coordinated cascade of hemostasis, inflammation, proliferation, and remodeling. Fibroblast migration, angiogenesis, extracellular matrix deposition, epithelialization, and collagen remodeling are tightly regulated by cytokines, growth factors, and molecular mediators. Any dysregulation within these pathways may culminate in chronic wound formation. Conventional wound management strategies including debridement, infection control, moisture balance, and dressing optimization are largely supportive rather than biologically restorative. Consequently, increasing attention has been directed toward biologically active adjunctive therapies capable of modulating cellular wound-healing pathways.

Vitamin A and its active metabolite retinoic acid regulate epithelial differentiation, immune response, collagen synthesis, angiogenesis, and fibroblast proliferation through retinoic acid receptors and retinoid X receptors. Experimental studies have demonstrated enhanced epithelialization, improved collagen deposition, and reversal of corticosteroid-induced suppression of wound healing following retinoid administration.

Despite compelling experimental evidence, robust randomized clinical trials evaluating topical retinoic acid in chronic wound healing remain limited. The present study was therefore undertaken to evaluate the efficacy of short-contact topical 0.05% retinoic acid ointment in chronic non-healing wounds compared with standard saline dressings.

MATERIALS AND METHODS

Study Design and Setting:

This prospective randomized controlled trial was conducted in the Department of General Surgery at Akash Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India.

Study Population:

Fifty patients presenting with chronic non-healing ulcers of varying etiologies were enrolled following informed consent.

Inclusion Criteria:

Age ≥18 years
Chronic ulcer persisting beyond six weeks
Measurable wound dimensions
Willingness for serial follow-up

Exclusion Criteria:

Malignant ulcers
Pregnancy and lactation
Known retinoid hypersensitivity
Critical limb ischemia
Systemic retinoid therapy
Severe systemic sepsis

Randomization:

Patients were randomized into intervention and control groups using a computer-generated allocation sequence.

Intervention Protocol:

The intervention group received short-contact topical 0.05% retinoic acid ointment during alternate-day dressings. The control group received conventional saline dressings according to institutional protocol.

Outcome Measures:

Primary outcomes included reduction in wound surface area and wound depth. Secondary outcomes included time to achieve ≥50% reduction in wound area and depth, granulation tissue formation, and treatment tolerability.

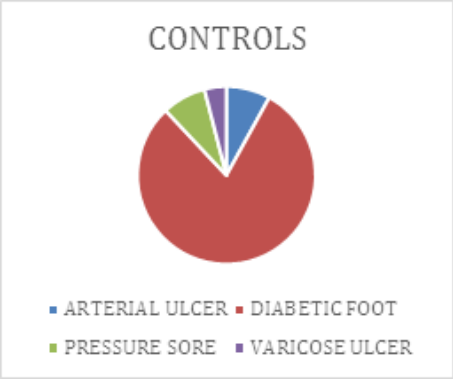
Statistical Analysis:

Continuous variables were expressed as mean ± standard deviation or

median with interquartile range as appropriate. Intergroup comparisons were performed using appropriate parametric and non-parametric tests. Friedman test analysis was used for serial within-group comparisons. Statistical significance was defined as $p < 0.05$.

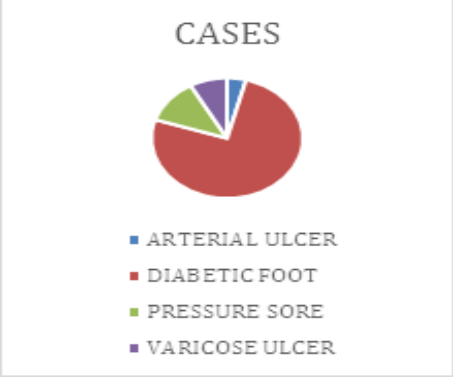
RESULTS

Baseline demographic characteristics including age distribution, gender distribution, ulcer duration, and wound dimensions were comparable between groups. Diabetic ulcers represented the predominant ulcer subtype in both cohorts.



Graph 3: Etiological distribution of chronic ulcers in the control group.

Pie chart illustrating the proportion of ulcer etiologies among control participants, including arterial ulcers, diabetic foot ulcers, pressure sores, and varicose ulcers. Diabetic foot ulcers constituted the majority of cases in this group.



Graph 4: Etiological distribution of chronic ulcers in the intervention (case) group.

Pie chart demonstrating the distribution of ulcer etiologies among patients receiving topical vitamin A therapy, including arterial ulcers, diabetic foot ulcers, pressure sores, and varicose ulcers. Diabetic foot ulcers represented the largest proportion of ulcers in the case group.

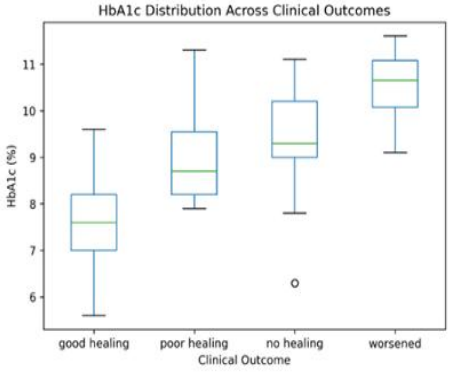
Serial wound assessment demonstrated significantly greater reduction in wound area among patients treated with topical retinoic acid compared with controls over four weeks. Intervention-group wounds demonstrated accelerated wound contraction and earlier granulation tissue formation.

Table : Remarks cross tabulation of cases and controls

cases/control * Remarks Crosstabulation								
Count								
	Remarks							
	good healing	lost to follow up	no healing	poor healing	underwent amputation	Worsened	Total	
cases/control	Cases	20	1	1	2	1	0	25
	Control	3	2	8	9	0	3	25
Total		22	3	8	10	1	3	50

Table shows the distribution of healing outcomes among the case and control groups. A higher proportion of patients in the vitamin A group demonstrated good healing compared with the control group, whereas poor healing and non-healing outcomes were more frequent in the control group.

Patients receiving retinoic acid achieved earlier ≥50% reduction in wound depth compared with the control cohort. Elevated HbA1c values correlated with slower wound healing outcomes overall; however, the intervention group nevertheless demonstrated superior healing dynamics.



Graph :Box-and-whisker plot illustrates baseline HbA1c distribution across clinical outcome categories. Median values are indicated by horizontal lines, with boxes representing interquartile ranges.

Table : Time-to-50% Reduction Analysis – wound depth

T50 defined as the first week at which ≥50% reduction from baseline was achieved

Group	Median time to 50% reduction (weeks)	p value
Case	2 weeks	0.0011
Control	3 weeks	

Mann–Whitney U (two-sided)

Table shows the comparison of time required to achieve 50% reduction in wound depth between the two groups. The case group achieved earlier reduction in wound depth compared with the control group.

Table : Time-to-50% Reduction Analysis – wound area

Group	Median time to 50% reduction (weeks)	p value
Case	2 weeks	0.14
Control	4 weeks	

Mann–Whitney U (two-sided)

Table shows the comparison of time required to achieve 50% reduction in wound area between the two groups. Although the median time was shorter in the intervention group, the difference did not reach statistical significance.

No clinically significant local irritation, hypersensitivity reactions, or evidence of systemic retinoid toxicity was documented during the study period.

DISCUSSION

The present randomized controlled trial demonstrated that short-contact topical retinoic acid significantly improved healing outcomes in chronic non-healing wounds compared with standard saline dressings. These findings are biologically plausible because retinoic acid regulates fibroblast proliferation, epithelial regeneration, collagen synthesis, angiogenesis, and inflammatory modulation.

Accelerated reduction in wound depth observed in the intervention cohort suggests enhanced granulation tissue formation and improved proliferative-phase activity. Retinoic acid appears to facilitate transition from persistent inflammation toward active tissue regeneration through regulation of cytokine signaling and extracellular matrix remodeling.

Previous experimental investigations by Hunt and Ehrlich demonstrated improved collagen synthesis and epithelialization

following vitamin A administration. Chithra et al. additionally reported increased hydroxyproline content and collagen maturation in retinoid-treated wounds. Wicke et al. further demonstrated improved granulation tissue formation and angiogenic response.

The present study also demonstrated favorable tolerability and absence of clinically significant adverse effects, supporting the feasibility of short-contact topical retinoic acid as an inexpensive adjunctive modality in resource-limited healthcare settings.

Limitations of the study include relatively small sample size, single-centre design, limited duration of follow-up, and absence of molecular wound-healing markers. Future multicentric randomized trials incorporating histopathological and biomarker analysis are warranted.

CONCLUSION

Short-contact topical 0.05% retinoic acid demonstrated statistically significant and clinically meaningful improvement in healing outcomes among patients with chronic non-healing wounds. The intervention was associated with accelerated wound contraction, earlier granulation tissue formation, and superior reduction in wound depth compared with conventional saline dressings.

Topical retinoic acid appears to represent a safe, inexpensive, and biologically active adjunctive therapy in chronic wound management and warrants further evaluation in larger multicentric studies.

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