e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 696-702

Original Research Article

Comparative Effectiveness Randomised Controlled Trial of Topical Ozone Gas Therapy Compared To Vacuum Assisted Closure in Healing of Diabetic Foot Ulcers: A Cost Effectiveness Study with Superiority Hypothesis

Bapathu Sai Teja Reddy[1], Mukesh Kumar Maheshwari[2], Sandeep Kansal[3], Aditya Rastogi[4], Nair Dhiren Ajit[5]

[1]Junior Resident, Department of General Surgery, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

[2]Professor, Department of General Surgery, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

[3]Professor, Department of General Surgery, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

[4]Associate Professor, Department of General Surgery, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

[5]Associate Professor and Officiating Principal & Dean, Faculty of AYUSH, Maharishi Aurobindo Subharti College and Hospital of Naturopathy and Yogic Sciences, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026

Corresponding author: Dr. Bapathu Sai Teja Reddy

Conflict of interest: Nil

Abstract

Background: Diabetic foot ulcers cause infection, delayed healing, prolonged hospitalization, limb loss, and treatment expenditure. Topical ozone gas therapy and vacuum-assisted closure (VAC) are adjunctive modalities, but comparative evidence remains limited.

Objectives: To compare ozone therapy and VAC for wound healing, granulation tissue formation, hospital stay, safety, healing outcome, and treatment cost.

Materials and Methods: This randomized controlled trial included 30 adults with type 1 or type 2 diabetes mellitus and Wagner grade 2, grade 3, or post-debridement grade 4 ulcers. Participants were randomly allocated to ozone therapy or VAC, with 15 patients in each group. All received debridement, glycaemic control, infection management, and care. Continuous variables were analysed using the independent-samples t-test, with Welch's correction where required, and categorical variables using the chi-square test.

Results: Mean wound-area reduction was greater with ozone than VAC (0.83 ± 0.18 versus 0.33 ± 0.13 cm²), with percentage reductions of 17.36 ± 6.16% and 6.45 ± 3.56%, respectively (both $p<0.001$). Healthy granulation occurred in 66.7% versus 40.0% ($p=0.143$). Hospital stay was shorter with ozone (7.00 ± 0.85 versus 11.8 ± 2.62 days; $p<0.001$). Bleeding and skin irritation were less frequent with ozone. Complete healing occurred in 40.0% of VAC-treated patients and none receiving ozone ($p=0.006$). Total cost was ₹7,140 ± 755 with ozone and ₹16,000 ± 0 with VAC ($p<0.001$).

Conclusion: Ozone therapy achieved greater wound reduction, fewer adverse effects, shorter hospitalization, and lower cost, whereas VAC produced a higher complete-healing rate.

Keywords: Diabetic Foot Ulcer; Ozone Therapy; Vacuum-Assisted Closure; Wound Healing; Cost-Effectiveness.

DOI: 10.25258/ijcpr.18.8.107

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Introduction

Diabetic foot ulceration is a difficult and costly complication of diabetes requiring prolonged wound care. In an Indian comparative study, adding topical ozone gas to conventional management produced faster microbial negativity and ulcer healing, shorter hospital stay, and fewer revision procedures than conventional care alone. [1] A network meta-analysis of randomised trials evaluated gas therapies using healing rate, ulcer-area reduction, healing time, amputation, and

adverse events, showing a heterogeneous evidence base. [2] A systematic review subsequently described ozone as promising but emphasised the need for better-designed studies. [3] Short-term ozone therapy has been evaluated in patients with type 2 diabetes and foot ulcers. After one week, ozone-treated patients had higher vascular endothelial growth factor and antioxidant indices and lower inflammatory markers and bacterial types; follow-up showed higher healing, shorter inpatient and antibiotic duration, and lower reinfection and readmission rates. [4] Comprehensive ozone therapy has also been assessed through wound size, ulcer grade, healing time, fasting glucose, and inflammatory biomarkers, although optimal methods require further investigation. [5]

Negative pressure wound therapy provides an established comparator. The German DiaFu-RCT found no significant overall advantage over standard moist wound care for wound closure within 16 weeks, although time to 95% granulation was shorter among patients with small wounds. [[6] An Indian randomised study reported earlier ulcer-size reduction, greater granulation, shorter hospital stay, and complete healing with negative pressure therapy. [7] Another trial found shorter preparation time before split-thickness skin grafting, better graft survival, and greater wound perfusion than alginate dressings. [8] Conversely, a systematic review found that ozone improved wound area and reduced amputation but did not significantly improve complete healing or hospital stay; evidence quality remained limited. [9]

The clinical burden is substantial: reported five-year mortality was 30.5% after diabetic foot ulceration, 46.2% after minor amputation, and 56.6% after major amputation. [10] Therefore, direct randomised comparison of topical ozone gas and VAC therapy is required to clarify relative healing, granulation, hospital-stay, safety, and cost outcomes in the Indian hospital setting.

Material and Methods

Study Design and Setting: A comparative randomised controlled trial was conducted at Subharti Hospital, India, to assess topical ozone gas therapy against vacuum-assisted closure (VAC) in non-healing diabetic foot ulcers.

Study Population and Sample Size: Thirty adult patients with type 1 or type 2 diabetes mellitus were enrolled and randomly allocated into two equal groups. Group A included 15 patients treated with topical ozone gas therapy, while Group B included 15 patients treated with VAC therapy. The sample size was determined according to feasibility and availability of eligible patients.

Inclusion Criteria: Patients of either sex, aged above 18 years, with Wagner grade 2, grade 3, or post-debridement grade 4 diabetic foot ulcers were included. Patients with venous insufficiency, lymphatic obstruction, or spreading cellulitis were not eligible.

Exclusion Criteria: Pregnant women, patients with foot gangrene and patients with active bleeding from the wound were excluded. Participants could withdraw consent at any stage, including because of treatment intolerance.

Treatment Protocol: All patients received standard wound care comprising surgical debridement, glycaemic control, infection management, and supportive treatment. In the ozone group, the affected limb was enclosed in an ozone-resistant bag, and ozone gas at 10–80 µg/mL was administered for 20–30 minutes. The VAC group wound was filled with sterile foam or gauze, secured with an adhesive drape, and attached to a suction device that applied continuous negative pressure of 75 to 125 mmHg. Dressings were changed at 48–72 hour intervals.

Data Collection and Outcomes: Baseline demographic, clinical, glycaemic and ulcer characteristics were collected. Results were reduction in wound area, percentage reduction in wound, formation of healthy granulation tissue, length of hospital stay, final healing status, adverse effects and cost of treatment.

Ethical Considerations: Written informed consent and Institutional Review Board approval were obtained. The study followed the principles of the Declaration of Helsinki.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation and compared using the independent-samples t-test, with Welch's correction where required. Categorical variables were analysed using the chi-square test. A p-value <0.05 was considered statistically significant.

Results

Table 1: Comparative Wound Healing (Primary Outcome) (n = 30).

Parameter	Ozone	VAC	p-value
Reduction (cm^2)	0.83 ± 0.18	0.33 ± 0.13	<0.001
% Reduction	17.36 ± 6.16	6.45 ± 3.56	<0.001

Statistical test: Independent t-test

The mean decrease in wound area was significantly greater in the topical ozone therapy group than in the VAC therapy group (0.83 ± 0.18 cm 2 vs. 0.33 ± 0.13 cm 2). The percentage decrease in wound area was also greater in the topical ozone therapy group than in the VAC therapy group (17.36 ± 6.16% vs. 6.45 ± 3.56%) (Table 1). Both differences were statistically significant ($p < 0.001$), indicating superior wound-healing efficacy with ozone therapy.

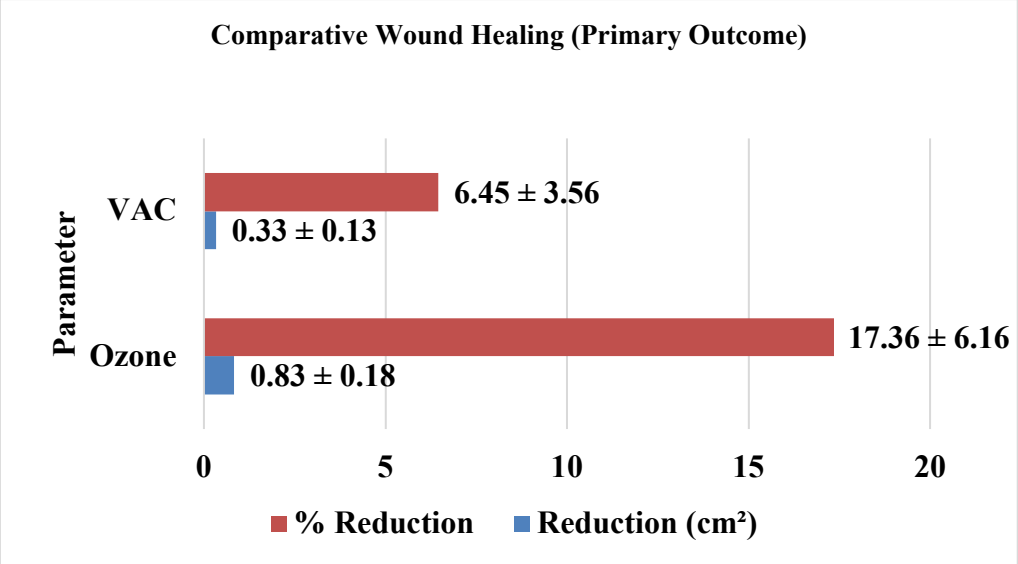

Figure 1: Comparative Wound Healing (Primary Outcome)

Table 2: Comparison of Granulation Tissue Status at Completion of Treatment between Ozone Therapy and VAC Therapy Groups (n = 30).

Granulation Tissue Status at Completion of Treatment	Ozone Therapy (n = 15)	VAC Therapy (n = 15)	Total (n = 30)	p-value
Healthy	10 (66.7%)	6 (40.0%)	16 (53.3%)	
Moderate	5 (33.3%)	9 (60.0%)	14 (46.7%)	
Total	15 (100.0%)	15 (100.0%)	30 (100.0%)	0.143

Statistical test used: Chi-square test ($\chi^2 = 2.143$, df = 1).

Table 2 shows that healthy granulation tissue was more frequent following ozone therapy than VAC therapy (66.7% versus 40.0%), whereas moderate granulation predominated in the VAC group (60.0% versus 33.3%). However, the between-group difference was not statistically significant ($\chi^2 = 2.143$, df = 1, p = 0.143), indicating a favourable numerical trend toward ozone therapy.

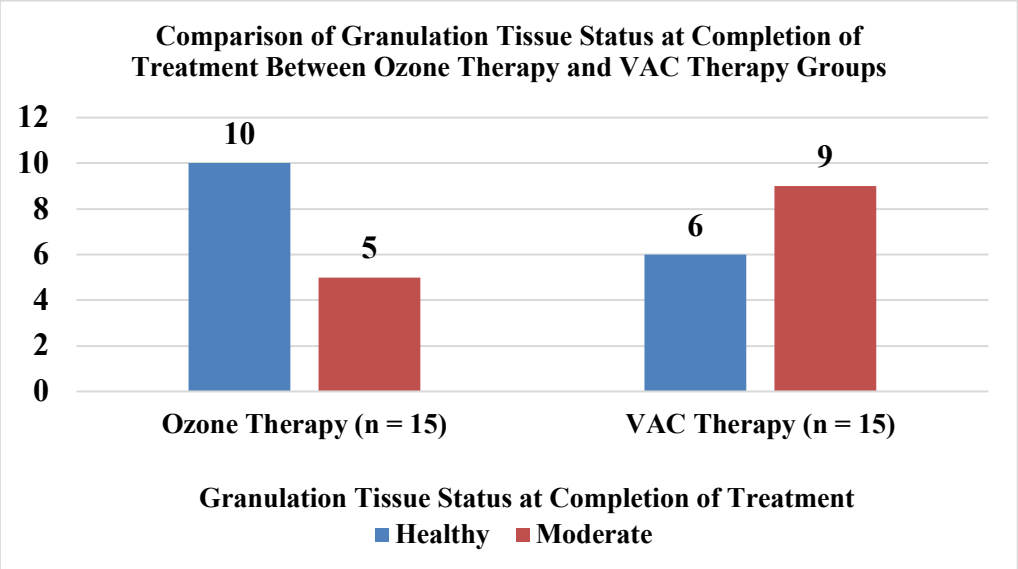

Figure 2: Comparison of Granulation Tissue Status at Completion of Treatment between Ozone Therapy and VAC Therapy Groups

Table 3: Comparison of Duration of Hospital Stay Between Ozone Therapy and VAC Therapy Groups (n = 30)

Parameter	Ozone Therapy (n = 15) Mean ± SD	VAC Therapy (n = 15) Mean ± SD	p-value
Hospital stay (days)	7.00 ± 0.85	11.8 ± 2.62	<0.001

Statistical test used: Independent samples t-test (Welch's correction applied).

Table 3 shows that the mean duration of hospital stay was significantly shorter among patients receiving topical ozone therapy than among those treated with VAC therapy (7.00 ± 0.85 days versus 11.8 ± 2.62 days). The difference was statistically significant ($p < 0.001$), indicating reduced hospitalisation with topical ozone therapy.

Table 4: Safety Profile (n = 30)

Event	Ozone	VAC	Total	p-value
Bleeding	0	8	8	0.002
Skin irritation	3	15	18	<0.001
Ozone intolerance	1	0	1	1.00

Statistical test: Chi-square.

Table 4 demonstrates that bleeding was absent in the ozone group but occurred in eight VAC-treated patients ($p = 0.002$). Skin irritation was also significantly less frequent with ozone therapy than with VAC therapy (3/15 versus 15/15; $p < 0.001$). Ozone intolerance occurred in one patient, without a significant between-group difference ($p = 1.00$).

Table 5: Comparison of Final Wound Healing Outcomes between Ozone Therapy and VAC Therapy Groups (n = 30).

Outcome	Status	Ozone Therapy (n = 15)	VAC Therapy (n = 15)	Total (n = 30)	p-value
Complete Healing	No	15 (100.0%)	9 (60.0%)	24 (80.0%)	
	Yes	0 (0.0%)	6 (40.0%)	6 (20.0%)	**0.006**
Partial Healing	No	3 (20.0%)	7 (46.7%)	10 (33.3%)	
	Yes	12 (80.0%)	8 (53.3%)	20 (66.7%)	**0.121**
Non-Healing	No	12 (80.0%)	14 (93.3%)	26 (86.7%)	
	Yes	3 (20.0%)	1 (6.7%)	4 (13.3%)	**0.283**

Statistical Test Used: Chi-square test

Table 5 shows that complete healing occurred significantly more often with VAC therapy than with ozone therapy (40.0% versus 0.0%; $p = 0.006$). Partial healing was more frequent in the ozone group (80.0% versus 53.3%), while non-healing occurred in 20.0% and 6.7%, respectively; however, these differences were not statistically significant.

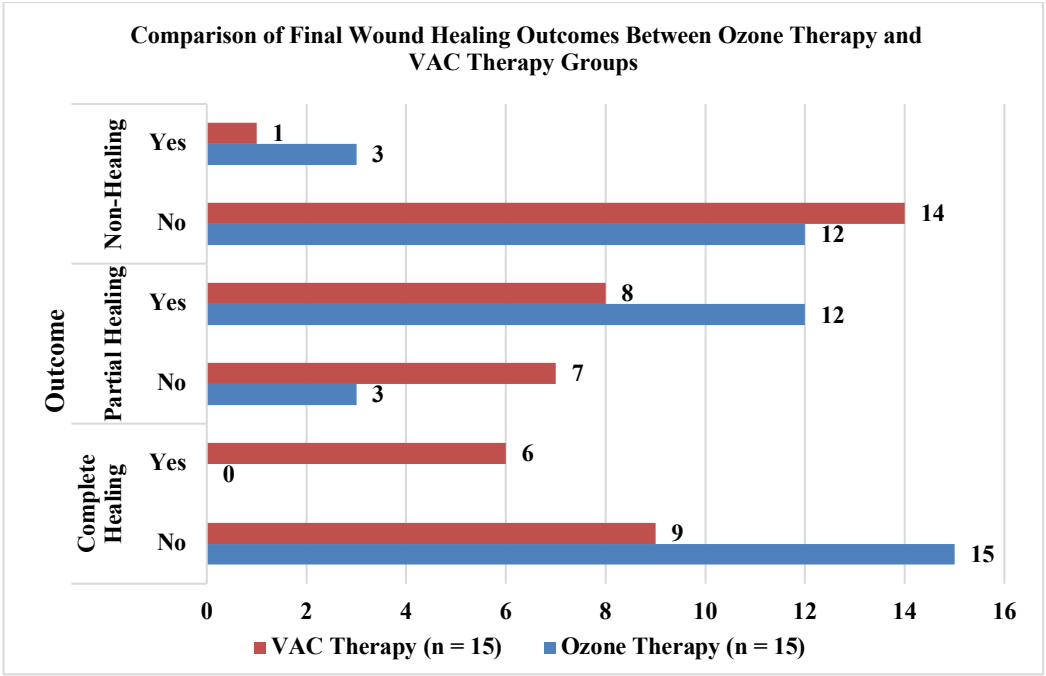

Figure 3: Comparison of Final Wound Healing Outcomes between Ozone Therapy and VAC Therapy Groups

Table 6: Inter-group Comparison of Treatment Cost Components between Ozone Therapy and VAC Therapy Groups (n = 30).

Cost Component	Ozone Therapy (n = 15) Mean ± SD (₹)	VAC Therapy (n = 15) Mean ± SD (₹)	p-value
Ozone Therapy Cost	2193 ± 194	7107 ± 532	<0.001
Dressing Cost	907 ± 103	2800 ± 189	<0.001
Hospital Cost	4040 ± 463	6093 ± 708	<0.001
Total Cost	7140 ± 755	16000 ± 0	<0.001

Statistical Test Used:

Independent samples t-test (Welch's correction applied where variance inequality was present) Table 6 demonstrates that all treatment-related costs were significantly lower in the ozone therapy group than in the VAC group. Mean therapy, dressing, hospital, and total costs were ₹2,193, ₹907, ₹4,040, and ₹7,140, respectively, compared with ₹7,107, ₹2,800, ₹6,093, and ₹16,000 for VAC therapy (all $p < 0.001$).

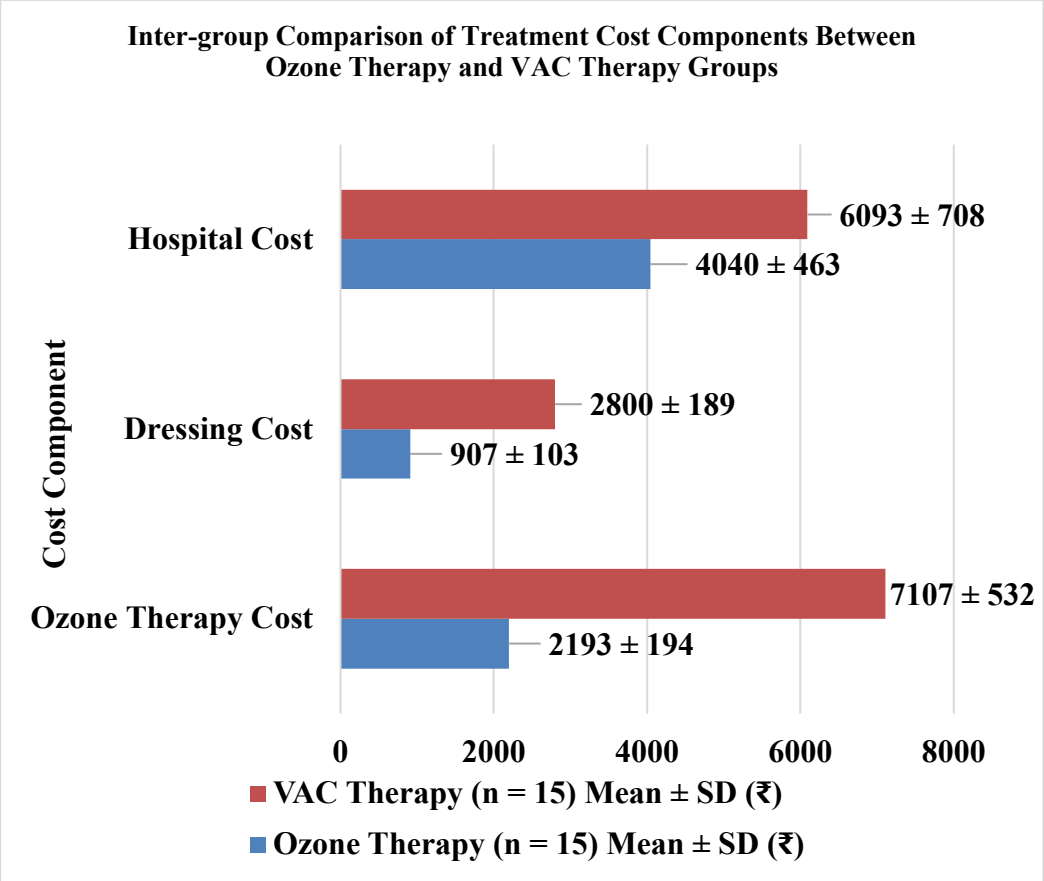

Figure 4: Inter-group Comparison of Treatment Cost Components between Ozone Therapy and VAC Therapy Groups

Discussion

Ozone showed a significantly higher reduction of wound area than VAC in absolute area (0.83+/-0.18 vs. 0.33+/-0.13 cm(2)) as well as in percentage reduction (17.36+/-6.16% vs. 6.45+/-3.56%; p<0.001). This is in agreement with the results of Dhamnaskar et al., (2021) [1] who reported a reduction of 32.37% compared to 17.15% on day 21 (p=0.01) and Wen et al., (2022) [9] who observed significant wound-area improvement (SMD=66.54%; p<0.00001). It's also good for healing. Sun et al. (2024) [4]; Filho et al (2024) [3]; Maranna et al (2021) [7] reported a reduction of 40.78% vs 21.18% (p=0.008) with NPWT. No superiority was found Seidel et al (2020) [6].

66.7% of the ozone treated patients and 40.0% of the VAC treated patients had healthy granulation while 33.3% and 60.0% of the patients respectively had moderate granulation. The difference was not statistically significant ($\chi 2=2.143$, p=0.143). This numerical superiority is corroborated with results of Dhamnaskar et al (2021)1 on faster granulation and Sun et al (2024)4 on better angiogenic and oxidative profile with better healing. In addition, Filho et al. (2024)3 reported the improvement of ulcer healing. However, Maranna et al [7] demonstrated significantly higher granulation rate

with NPWT as compared to saline dressings (91.14% vs. 52.61%; p<0.001). Wu et al [8] demonstrated better VAC mediated wound bed preparation.

Hospital stay was shorter in ozone group as compared to vacuum assisted closure (VAC) group (7.00±0.85 versus 11.8±2.62 days; p<0.001). This is in accordance to a study by Dhamnaskar et al., (2021) [1] who reported a decrease in the hospitalizations with the use of topical ozone therapy and Filho et al., (2024) [3] in a metanalysis who showed a decrease in the length of hospital stay of patients treated with ozone.

Sun et al. (2024) [4] reported that ozone therapy was also associated with shorter duration of hospital stay and antibiotic use. Wen et al.(2022) [9] however did not find a significant reduction in hospital stay with ozone . Maranna et al. (2021) [7] demonstrated the hospital stay was shorter with NPWT than saline dressings (15.68 days vs 29.00 days). Therefore, VAC may reduce the length of stay of inpatient compared with conventional care.

Bleeding was absent in the ozone group but occurred in 8 of 15 VAC-treated patients, while skin irritation affected 3 of 15 ozone recipients and all 15 VAC recipients; both differences were significant (p=0.002 and p<0.001, respectively). Ozone intolerance occurred in 1 patient with no significant difference between groups (p=1.00). Topical ozone was well tolerated 1 and no adverse events related to ozone were reported. In the study of Sun et al. (2024) [4], also the rates of reinfection and re-admission declined. In Seidel et al. (2020) [6] higher incidence of adverse events was reported in NPWT, but few were treatment related.

Complete healing occurred in 6 of 15 VAC-treated patients (40.0%) but in none of the ozone-treated patients (p=0.006). Partial healing was more frequent with ozone than VAC (80.0% versus 53.3%; p=0.121), whereas non-healing occurred in 20.0% and 6.7%, respectively (p=0.283).

The percentage of complete healing at 3 months was significantly higher in NPWT group than saline dressings group (90.9% vs. 26.1%) (Maranna et al. 2021)[7]. Wu et al. (2023) [8] showed that the VAC was better in preparing the wound bed.

Wen et al. (2022)9 O3 No major improvement in total healing. However, complete closure of all patients treated with ozone has been observed by Izadi et al. (2019)[5] and better complete healing in patients treated with ozone has been observed by Filho et al. (2024) [3]. Duration of treatment, comparator therapy and endpoint assessment were highly heterogeneous. All treatment-related costs were significantly lower with ozone therapy. Mean therapy, dressing, hospital, and total costs were ₹2,193 ± 194, ₹907 ± 103, ₹4,040 ± 463, and ₹7,140 ± 755, respectively, compared with ₹7,107 ± 532, ₹2,800 ± 189, ₹6,093 ± 708, and ₹16,000 ± 0 for VAC therapy (all p<0.001). Dhamnaskar et al. (2021) [1] Shorter hospitalization and reoperations in ozone treated patients Sun et al. (2024) [4] Less hospitalization i.e. less use of resources. Armstrong et al (2020) [10] showed a high economic burden of diabetic foot complications but did not make direct monetary comparisons.

Conclusion

This randomized controlled trial demonstrated that topical ozone gas therapy produced significantly greater short-term wound-area reduction than vacuum-assisted closure, with mean absolute and percentage reductions of 0.83 ± 0.18 cm² and 17.36 ± 6.16%, respectively, compared with 0.33 ± 0.13 cm² and 6.45 ± 3.56% with VAC. Ozone therapy was also associated with more healthy granulation tissue, shorter hospitalization, fewer bleeding and skin-irritation events, and substantially lower treatment expenditure. However, complete healing occurred only in the VAC group, whereas partial healing predominated after ozone therapy, indicating that early wound reduction and final closure may not reflect the same therapeutic advantage. Topical ozone therefore appears to be a safe, economical, and clinically useful option for accelerating early healing and reducing resource utilization in non-healing diabetic foot ulcers, while VAC may remain preferable for achieving complete closure in selected wounds. Larger, adequately powered trials with standardized treatment duration and follow-up are required.

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