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Wound Healing Efficacy of Topical Papaverine Dressing in Ischemic Diabetic Foot Wounds: A Pilot Study

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Abstract

Background

Ischemic diabetic foot wounds remain difficult to heal despite standard wound care. Papaverine has vasodilatory properties, but its role in ischemic diabetic foot wounds has not been established. This randomized study evaluated topical papaverine as an adjunct to standard wound care.

Methods

A prospective, single-centre, randomized, placebo-controlled study included 30 participants with ischemic diabetic foot wounds. Participants were randomized 1:1 to topical papaverine (30 mg/mL) plus standard wound care or normal saline placebo plus standard wound care. The primary outcome was healthy granulation by 30 days. Participants, investigator, and outcome assessor were blinded.

Results

Fifteen participants were allocated to each group, with one control participant withdrawing on postoperative day 5. Healthy granulation occurred in 8/15 (53.3%) participants in the papaverine group and 4/14 (28.6%) evaluable participants in the control group (P=0.264). In the longitudinal analysis, the overall group effect (P = 0.142) and group × week interaction (P = 0.285) were not statistically significant; none of the between-group comparisons at individual weeks remained significant after Holm adjustment. Time to healthy granulation did not differ significantly between groups (log-rank P=0.204). No study-related adverse events or serious adverse events were reported during the study period.

Conclusion

Topical papaverine was associated with greater wound-area reduction at Week 2, but this difference was not sustained at subsequent assessments, and the primary outcome did not differ significantly between groups. These preliminary findings do not establish efficacy and should be interpreted cautiously. Larger randomized trials with standardized wound assessment are needed.

Categories: Therapeutics, General Surgery, Endocrinology/Diabetes/Metabolism
Keywords: diabetic foot ulcer, ischemic wound, papaverine, randomized controlled trial, wound healing

Introduction

Diabetic foot ulcers (DFUs) represent a serious complication of diabetes and are associated with recurrent ulceration, infections, hospitalizations, lower-extremity amputation, and decreased quality of life. Peripheral neuropathy, mechanical stress, infection, poor tissue repair, and peripheral arterial disease (PAD) all play a role in their development and persistence [1]. PAD is especially significant in people with diabetes and a foot ulcer, occurring in about half of this population and being associated with poor limb and cardiovascular outcomes [2].

Good tissue perfusion is essential for wound healing, and PAD can negatively affect the healing potential of DFUs. Management involves ongoing assessment and treatment of arterial disease, infection management, offloading, metabolic optimization, and wound debridement [2]. However, healing remains difficult, and a recent systematic review reported that the level of evidence for most interventions aimed at improving DFU healing was low or very low, suggesting the need for more appropriately designed clinical trials [3].

Papaverine is a peripheral vasodilator and a nonselective phosphodiesterase inhibitor. It has been associated with increased cyclic adenosine monophosphate and cyclic guanosine monophosphate activity and modulation of vascular smooth muscle contraction [4]. Experimental studies have shown that papaverine

can inhibit vasoconstriction by affecting intracellular calcium, myosin light-chain phosphorylation, and actin cytoskeletal dynamics [5]. It has also been reported that, in surgical applications, local administration of papaverine can increase vascular blood flow [5,6]. Experimental models have demonstrated a positive effect of topical papaverine on tissue blood flow and skin-flap survival, while a papaverine-loaded hydrogel formulation has shown similar effects in a rat skin-flap model [7,8].

However, findings from vascular and experimental flap models cannot be directly applied to ischemic diabetic foot wounds. Topical papaverine may therefore have potential as a vasodilatory adjunct and warrants further study for its role in wound healing in this population. The aim of the present pilot randomized study was to investigate whether topical papaverine, when combined with standard wound care, could promote healthy granulation tissue formation and improve wound-area reduction in patients with ischemic diabetic foot wounds over a 30-day period. Study-related adverse events and serious adverse events were also assessed.

Materials And Methods

Study design and setting

This was a prospective, single-centre, randomized, parallel-group, placebo-controlled pilot study conducted at Surya Hospital, Kolhapur, India. A total sample size of 30 participants (15 per group) was selected for this pilot study and randomized in a 1:1 ratio, with 15 participants allocated to each group. The study was registered prospectively with the Clinical Trials Registry-India (CTRI/2025/01/079660) on 28 January 2025. Institutional Ethics Committee approval was obtained on 28 December 2024.

Participants

Patients admitted to Surya Hospital with ischemic diabetic foot wounds were recruited using purposive sampling. Participants aged 30-80 years of either sex were eligible. Ischemic diabetic foot wounds were identified at the initial consultation based on predefined clinical and diagnostic eligibility criteria. Ischemia was assessed based on clinical examination and vascular investigations, including ankle-brachial index (ABI) and Colour Doppler ultrasonography. An ABI <0.90 was considered indicative of ischemia, while monophasic flow in the distal limb arteries supplying the wound was considered an abnormal Doppler finding [9]. All 30 patients included in the study demonstrated monophasic Doppler waveforms. The Doppler examinations were performed using the same machine and reported by a single radiologist. No predefined numerical peak systolic velocity (PSV) cutoff was used for study eligibility. Pale granulation and critical limb ischemia in patients who had not undergone vascular intervention because of an informed decision were also considered during the clinical assessment. Patients unwilling to provide consent, those who had undergone angioplasty, and those with good blood supply to the wound were excluded.

Surgical debridement was performed, and anti-infective, metabolic, antidiabetic, and drugs intended to increase vascular flow were administered as part of standard care and hospital protocols. Topical oxygen therapy was initiated from the first postoperative day.

Randomization and blinding

The randomization sequence was computer-generated. Participants were allocated in a 1:1 ratio to either topical papaverine dressing plus standard wound care or placebo dressing with normal saline plus standard wound care. Allocation was concealed using sequentially numbered, sealed, opaque envelopes. Participants, the investigator, and the outcome assessor were blinded to treatment allocation. For each dressing, the clinical investigator received a coded syringe containing either papaverine or normal saline according to the allocation sequence, with treatment identity concealed from personnel performing the dressing and collecting wound-assessment data.

Intervention and comparator

The dressing protocol was initiated approximately 24 hours after surgery. Before each dressing, the wound was cleaned with normal saline and mopped with sterile gauze. The allocated study solution was then sprayed over the wound bed and wound margins using a 100-unit insulin syringe, maintaining a non-contact technique. The application technique was modified from the topical papaverine spraying method described by Gowda et al. [6]. The intervention group received papaverine (30 mg/mL) at a protocol-specified nominal volume of 1 mL per 2-2.5 cm^2 of wound area, while the control group received normal saline using the same application procedure. The concentration corresponded to an available injectable formulation, and the area-based application regimen was intended to provide a consistent nominal volume relative to wound size. This regimen was selected empirically, as no validated diabetic-foot-specific topical dose or formal dose-ranging evidence was available to establish an optimal concentration or area-based volume. The rationale for exploring topical papaverine was its local vasodilatory effect and the limited prior clinical evidence of topical application in ischemic tissue [10]. The wound was subsequently covered with sterile gauze and a standard dressing.

Dressings were repeated every 24 hours and continued for up to 30 days, corresponding to the predefined

observation period for the development of healthy granulation tissue. The once-daily schedule was selected as a pragmatic, standardized regimen synchronized with routine postoperative wound dressing, allowing regular local application and wound assessment while maintaining the same treatment frequency in both groups. This schedule was protocol-defined and was not based on established topical pharmacokinetic or dose-frequency optimization data.

The 30-day observation period was selected to evaluate early wound-healing response, particularly the development of healthy granulation tissue and reduction in wound area. Previous studies have shown that wound-area reduction over the first four weeks is predictive of subsequent healing in diabetic foot ulcers [11]. The IWGDF guidance also recommends reassessment when a diabetic foot ulcer fails to improve significantly, such as when wound area reduction is less than 50% after four weeks of appropriate care [2]. Accordingly, the 30-day period provided a clinically relevant timeframe for assessing progression from pale to healthy red or dark-pink granulation tissue, wound-size reduction, and early treatment response. Wounds that did not achieve protocol-defined healthy granulation within this period were classified as nonresponders at Day 30; this classification did not imply that the wounds were permanently non-healing.

Both groups received standard wound care throughout the study period, including routine wound management and other clinically indicated treatments according to hospital protocols. Topical oxygen therapy was initiated from the first postoperative day. During follow-up, wound size, granulation quality (pale, pink, or red), exudate (present or absent; serous or pus when present), and surrounding edema were assessed. The postoperative day on which healthy granulation was first observed was also recorded. Earlier development of healthy granulation could lead to preparation for grafting or progression to healing by secondary intention, as clinically appropriate. Negative-pressure wound therapy (VAC), repeat debridement, and other interventions were directed by the treating clinicians according to the patient's clinical condition.

Outcome measures

Primary Outcome

The primary outcome was the achievement of healthy granulation tissue by Day 30. Healthy granulation was defined as a reduction in wound size accompanied by the development of a red or dark-pink wound colour. As per the protocol-defined criteria, non-healing was defined as failure of wound size to decrease by 1 mm per day in at least one dimension, together with the persistence of a pale wound.

Secondary Outcomes

The secondary outcomes included the requirement for skin grafting and the percentage reduction in wound area from baseline to the Week 4/Day 30 assessment window.

Exploratory wound-healing parameters

Additional exploratory wound-healing parameters included wound size, wound colour (pale, pink, or red), exudate (presence or absence, and serous or purulent character when present), surrounding edema, and the postoperative day on which healthy granulation tissue was first observed. The requirement for further wound closure or advanced wound-management procedures was also documented when clinically indicated.

Wound assessment and data handling

Wound measurements were recorded during clinically feasible wound-review visits. Wound photographs were obtained by the dressing provider, with a ruler used for calibration. Digital wound-area measurements were performed in cm^2 using WoundGenius (imito AG, Zurich, Switzerland) by a single independent assessor who was not involved in patient treatment and was blinded to treatment allocation. Before commencing wound assessments, the assessor received training from the study investigator, MB. The assessor delineated the wound margins using the software to calculate wound area at the available assessment time points. A single assessor performed all measurements to minimize interobserver variability.

Wound size was assessed on the first postoperative day and daily thereafter, as clinically feasible. Granulation tissue colour was assessed visually using the predefined three-category photographic colour-reference scale included in the approved study protocol (Figure *1*), with granulation classified as pale, pink, or red. Healthy granulation was defined as the presence of red or dark-pink granulation tissue accompanied by a reduction in wound size. Granulation colour assessment was performed separately from digital wound-area measurement. Wound size, colour, exudate, and surrounding edema were documented during follow-up, and the postoperative day on which healthy granulation was first observed was recorded. The visual assessment of wound characteristics was conceptually consistent with established wound-assessment principles described in the Bates-Jensen Wound Assessment Tool pictorial guide [12].

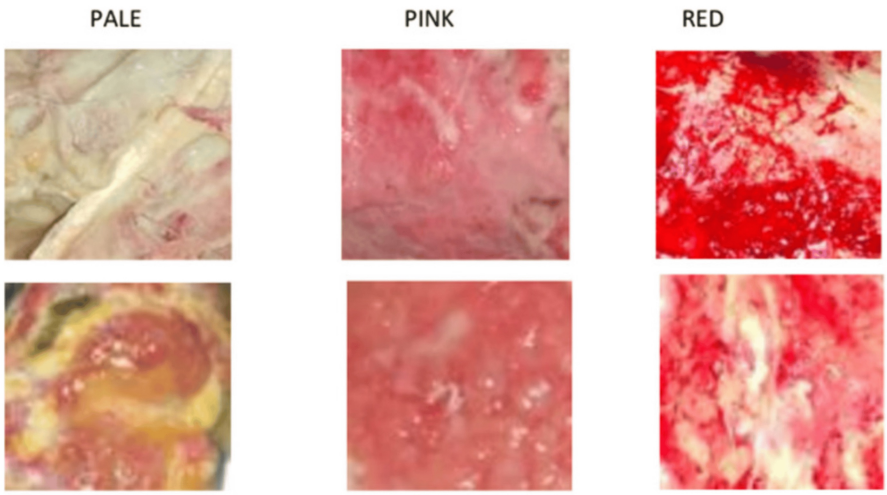


FIGURE 1: Photographic colour-reference scale for visual assessment of wound granulation tissue

Granulation tissue was classified as pale, pink, or red according to the predefined photographic reference scale included in the approved study protocol.

Baseline wound area was defined as the first available numeric measurement after the index procedure or initiation of dressing. The Week-4/Day-30 wound-area measurement was defined as the closest available numeric measurement obtained between days 25 and 35. Participants without both baseline and Week-4 window measurements were excluded from the Week-4 wound-area analysis but remained included in the clinical disposition and primary clinical outcome assessment. Extended follow-up, when available, was considered routine clinical care and was not included in the primary efficacy analysis.

Statistical analysis

The primary outcome, achievement of healthy granulation tissue by Day 30, was compared between the groups using Fisher's exact test. The analysis included participants with available Day-30 outcome data. The participant who withdrew from the control group on the fifth day was excluded because the primary outcome could not be assessed at Day 30.

Wound-area outcomes were analyzed using the available measurements. The percentage reduction in wound area at the fourth Week was compared between groups using the Mann-Whitney U test, while the proportion of participants who achieved at least a 50% reduction in wound area was compared using Fisher's exact test. These analyses were considered exploratory because of the small sample size and incomplete wound-area data.

Time to achievement of healthy granulation tissue was assessed separately using the Kaplan-Meier method. Participants who did not achieve healthy granulation were censored at their last available assessment. The participant who withdrew from the control group on the fifth day was censored at the time of withdrawal. This analysis was conducted separately from the primary Day-30 outcome analysis.

Safety assessment

Study-related adverse events and serious adverse events were recorded during the protocol-defined study period. Disease-related progression, additional debridement, amputation, skin grafting, vacuum-assisted closure, and other advanced wound-care procedures were managed according to routine diabetic-foot clinical care and were not considered study-related adverse events unless a causal relationship with the study intervention was identified.

Protocol deviations and changes

No changes were made to the eligibility criteria, intervention, comparator, or primary outcome after trial commencement. Irregular wound-area measurement timing and missing Week-4 measurements were handled using the analytical approach described.

Ethics

The study received Institutional Ethics Committee approval on 28 December 2024. Written informed consent

was obtained from all participants before enrollment. Informed consent forms and source documents were retained at the study site.

Results

A total of 144 patients were screened, of whom 41 were eligible and 11 declined participation. Thirty participants were enrolled and randomized equally to the topical papaverine plus standard wound care group (n=15) or the standard wound care group (n=15). One participant in the standard wound care group withdrew on postoperative Day 5 (Figure 2).

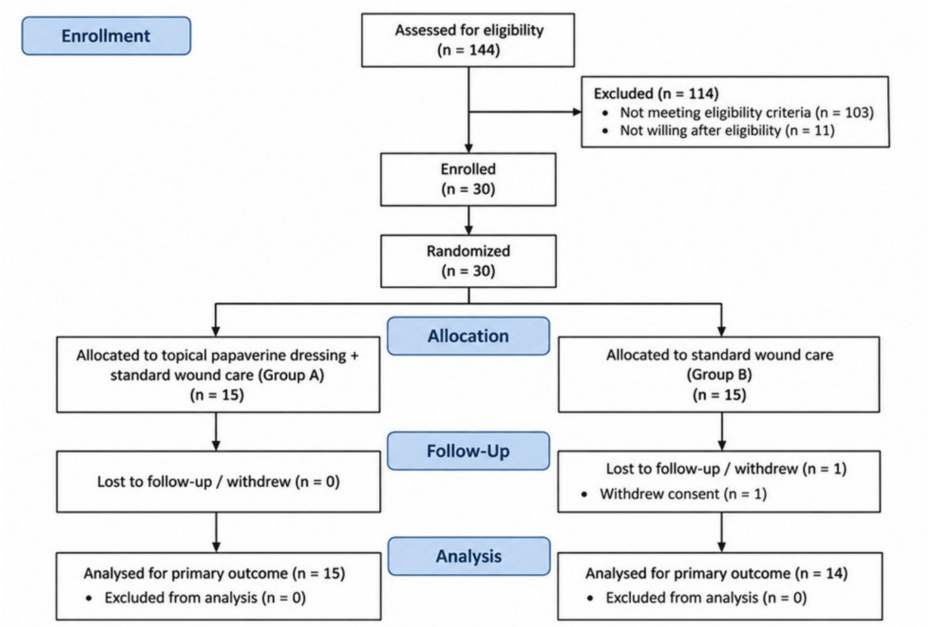


FIGURE 2: CONSORT flow diagram of participant recruitment, allocation, follow-up, and analysis

The baseline characteristics of the study participants are presented in Table 1. The mean age was 63.20 ± 9.58 years in the papaverine group and 60.43 ± 9.98 years in the control group. Males constituted 80.0% of participants in both groups. The mean body mass index was 24.60 ± 3.02 kg/m² in the papaverine group and 25.03 ± 4.46 kg/m² in the control group. The median duration of ulcer was 15 weeks (IQR, 10-60) and 30 weeks (IQR, 12.5-52.5), respectively. The median blood sugar level was 157 mg/dL (IQR, 135.65-225.50) in the papaverine group and 239 mg/dL (IQR, 169.50-296.00) in the control group. HbA1c was 9.74 ± 2.30% and 8.82 ± 1.89%, respectively. Regarding vascular parameters, the mean ankle-brachial index was 0.90 ± 0.06 in the papaverine group and 0.99 ± 0.26 in the control group. Hypertension was present in 93.3% and 80.0% of participants, respectively. Previous lower-limb amputation was reported in 46.7% of the papaverine group and 53.3% of the control group. Multiple ulcers were present in 60.0% and 20.0% of participants, respectively. Severe Wagner grade (Grade 3-4) was observed in 60.0% of participants in both groups. An ABI below 0.90 was observed in 6 (40.0%) participants in the papaverine group and 7 (46.7%) participants in the control group, while an ABI of 0.90 or above was observed in 9 (60.0%) and 8 (53.3%) participants, respectively.

Characteristic	Category / Summary	Papaverine group (n = 15)	Control group (n = 15)	Test statistic	p-value	SMD
Demographic characteristics						
Age, years	Mean ± SD	63.20 ± 9.58	60.43 ± 9.98	t = 0.762	0.453	0.331
Sex	Male	12 (80.0%)	12 (80.0%)	Fisher's Exact	1.000	0.000
	Female	3 (20.0%)	3 (20.0%)			
Diabetes and laboratory characteristics						
Body mass index, kg/m²	Mean ± SD	24.60 ± 3.02	25.03 ± 4.46	t = −0.307	0.761	0.112
Duration of diabetes,						

years	Mean ± SD	15.78 ± 8.87	11.58 ± 7.40	t = 1.388	0.177	0.582
Ulcer duration, weeks	Median (IQR)	15 (10–60)	30 (12.5–52.5)	U = 105.0	0.770	0.313
Blood sugar level	Median (IQR)	157 (135.65–225.50)	239 (169.50–296.00)	U = 79.5	0.178	0.366
HbA1c, %	Mean ± SD	9.74 ± 2.30	8.82 ± 1.89	t = 0.927	0.368	0.285
Hemoglobin, g/dL	Mean ± SD	10.50 ± 2.13	10.53 ± 2.22	t = −0.034	0.974	0.012
Neutrophil-to-lymphocyte ratio	Mean ± SD	6.72 ± 3.24	5.85 ± 3.60	t = 0.678	0.503	0.253
Serum creatinine, mg/dL	Median (IQR)	1.20 (1.02–1.35)	1.00 (0.86–1.51)	U = 87.0	0.300	0.380
eGFR, mL/min/1.73 m²	Median (IQR)	68.03 (45.96–72.47)	69.65 (50.41–82.00)	U = 87.0	0.300	0.392
CRP	Median (IQR)	65.64 (33.42–92.07)	14.60 (2.64–61.02)	U = 11.0	0.098	0.889
SpO_2, %	Median (IQR)	98 (97–98.5)	98 (98–98)	U = 101.5	0.633	0.234
Vascular assessment						
Ankle pressure, mmHg	Mean ± SD	116.67 ± 13.69	125.00 ± 30.17	t = −0.974	0.342	0.356
Brachial pressure, mmHg	Median (IQR)	130 (124.5–130)	125 (120–137.5)	U = 98.0	0.560	0.163
Ankle–brachial index	Mean ± SD	0.90 ± 0.06	0.99 ± 0.26	t = −1.319	0.206	0.482
Ankle–brachial index category	ABI below 0.90 n (%)	6 (40.0)	7 (46.7)	χ^2 = 0.136	0.713	0.135
	ABI 0.90 or above n (%)	9 (60.0)	8 (53.3)			
Comorbidities and risk factors						
Hypertension	No	1 (6.7%)	3 (20.0%)	Fisher's Exact	0.598	0.392
	Yes	14 (93.3%)	12 (80.0%)			
Tobacco use	No	14 (93.3%)	10 (66.7%)	Fisher's Exact	0.169	0.667
	Yes	1 (6.7%)	5 (33.3%)			
Smoking	No	15 (100.0%)	14 (93.3%)	Fisher's Exact	1.000	0.371
	Yes	0 (0.0%)	1 (6.7%)			
Alcohol use	No	15 (100.0%)	11 (73.3%)	Fisher's Exact	0.100	0.784
	Yes	0 (0.0%)	4 (26.7%)			
Previous lower-limb amputation	No	8 (53.3%)	7 (46.7%)	χ^2 = 0.133	0.715	0.172
	Yes	7 (46.7%)	8 (53.3%)			
Wound characteristics						
Multiple ulcers	No	6 (40.0%)	12 (80.0%)	Fisher's exact	0.060	0.816
	Yes	9 (60.0%)	3 (20.0%)			
Osteomyelitis	No	15 (100.0%)	12 (80.0%)	Fisher's exact	0.224	0.667
	Yes	0 (0.0%)	3 (20.0%)			
Ulcer side	Bilateral	1 (6.7%)	0 (0.0%)	Fisher's exact (Monte Carlo)	0.464	0.404
	Left	7 (46.7%)	10 (66.7%)			
	Right	7 (46.7%)	5 (33.3%)			
Wagner grade	Mild/Moderate (Grade 0–2)	6 (40.0%)	6 (40.0%)	χ^2 = 0.000	1.000	0.000
	Severe (Grade 3–4)	9 (60.0%)	9 (60.0%)			

TABLE 1: Baseline characteristics of study participants by group (n=30)

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. Independent-samples t-test was used for normally distributed continuous variables, Mann–Whitney U test for non-normally distributed continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate. SMD (Standardized Mean Difference) measures the magnitude of baseline differences between the two groups, independent of sample size. An absolute SMD <0.10 indicates negligible imbalance, 0.10–0.20 small imbalance, 0.20–0.50 moderate imbalance, and >0.50 substantial imbalance. SMD is a descriptive measure of baseline balance and should be interpreted independently of p-values. A two-sided p-value <0.05 was considered statistically significant.

BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; IQR: interquartile range; SD: standard deviation; SMD: Standardized Mean Difference; SpO_2: peripheral oxygen saturation; t: independent-samples t-test statistic; U: Mann–Whitney U test statistic; χ^2: chi-square test statistic.

At the 30-day follow-up, healthy granulation tissue was achieved in 8 of 15 participants (53.3%) in the papaverine group and 4 of 14 evaluable participants (28.6%) in the control group (RD, 24.8 percentage points; p = 0.264). VAC application within one month was required in 5 (33.3%) and 3 (21.4%) participants, respectively (RD, 11.9 percentage points; p = 0.682), while skin or skin-substitute grafting was performed in 2 (13.3%) participants in the papaverine group and none in the control group (RD, 13.3 percentage points; p = 0.483). The mean time to healthy granulation was 16.12 ± 10.06 days (n = 8) in the papaverine group and 10.25 ± 8.46 days (n = 4) in the control group (MD, 5.88 days; 95% CI, −7.12 to 18.88; P = 0.322). Mean hospital stay was 7.00 ± 3.84 days in the papaverine group and 5.79 ± 2.86 days in the control group (MD, 1.21 days; 95% CI, −1.36 to 3.78; p = 0.341) (Table 2).

Clinical outcome	Category / Summary	Papaverine group (n = 15)	Control group (n = 14)	Effect estimate (95% CI)	Test statistic	p-value
Healthy granulation at POD 30	Yes	8 (53.3%)	4 (28.6%)	RD +24.8 percentage points	Fisher's exact	0.264
	No/Pale granulation	7 (46.7%)	10 (71.4%)	—		
VAC application within 1 month	Yes	5 (33.3%)	3 (21.4%)	RD+11.9 percentage points	Fisher's exact test	0.682
	No	10 (66.7%)	11 (78.6%)	—		
Skin and skin substitute grafting within 1 month	Yes	2 (13.3%)	0 (0.0%)	RD+13.3 percentage points	Fisher's exact test	0.483
	No	13 (86.7%)	14 (100.0%)	—		
Day of healthy granulation (days)	Mean ± SD	16.12 ± 10.06 (n = 8)	10.25 ± 8.46 (n = 4)	MD: +5.88 days (95% CI: −7.12 to approximately 18.88)	t = 1.06	0.322
Length of hospital stay (days)	Mean ± SD	7.00 ± 3.84 (n = 15)	5.79 ± 2.86 (n = 14)	MD: +1.21 days (95% CI: −1.36 to approximately 3.78)	t = 0.971	0.341

TABLE 2: One-month follow-up status and healing outcomes by group

Data are presented as frequency and percentage or mean ± standard deviation (SD), as appropriate. One participant in the control group withdrew on postoperative Day 5 and was excluded from the primary outcome analysis because the Day-30 outcome was unavailable. Therefore, the primary outcome was assessed in 15 participants in the papaverine group and 14 evaluable participants in the control group. Fisher's exact test was used to compare healthy granulation, VAC application, and skin and skin substitute grafting between groups. Welch's independent-samples t-test was used for continuous outcomes. Time to healthy granulation was summarized among participants with available records (papaverine, n = 8; control, n = 4). All tests were two-sided, and a p-value <0.05 was considered statistically significant.

RD: risk difference; MD: mean difference; CI: confidence interval; VAC: vacuum-assisted closure; POD: postoperative day.

Among participants with available wound-area measurements, the mean baseline wound area was 7.83 ± 3.78 cm^2 in the papaverine group and 7.64 ± 4.51 cm^2 in the control group. The corresponding wound areas at Weeks 1 and 2 were 7.70 ± 3.50 cm^2 and 5.53 ± 2.32 cm^2 in the papaverine group, and 7.55 ± 4.63 cm^2 and 5.64 ± 3.21 cm^2 in the control group, respectively. At Week 3, the median wound area was 5.38 cm^2 (IQR, 4.51-6.13) in the papaverine group and 5.25 cm^2 (IQR, 5.01-6.23) in the control group. At Week 4, the corresponding values were 4.62 cm^2 (IQR, 4.02-5.58) and 4.34 cm^2 (IQR, 3.02-8.50), respectively. The mean percentage reduction in wound area from baseline was 0.68 ± 16.22% versus 3.83 ± 19.76% at Week 1, 27.17 ± 11.16% versus 13.78 ± 10.42% at Week 2, 27.63 ± 27.62% versus 10.98 ± 6.85% at Week 3, and 35.58 ± 23.35%

versus 23.44 ± 16.61% at Week 4 in the papaverine and control groups, respectively. At Week 4, two participants (20.0%) in the papaverine group and none in the control group achieved a ≥50% reduction in wound area, while 8 (80.0%) and 11 (100%), respectively, were classified as non-responders (Table 3).

Variable	Category	Papaverine group	Control group	Effect estimate (95% CI)	Test statistic	p-value
Wound area (cm²)	Baseline, mean ± SD	7.83 ± 3.78	7.64 ± 4.51	0.19 (−3.08 to 3.47)	t = 0.122	0.904
	Week 1, mean ± SD	7.70 ± 3.50	7.55 ± 4.63	0.15 (−3.21 to 3.51)	t = 0.092	0.928
	Week 2, mean ± SD	5.53 ± 2.32	5.64 ± 3.21	−0.11 (−3.34 to 3.12)	t = −0.073	0.943
	Week 3, mean ± SD	5.41 ± 1.08	6.14 ± 2.87	−0.74 (−4.23 to 2.76)	t = −0.537	0.614
	Week 4, mean ± SD	5.65 ± 2.96	6.07 ± 4.19	−0.42 (−3.73 to 2.88)	t = −0.268	0.792
Wound-area reduction (%)	Week 1, mean ± SD	0.68 ± 16.22	3.83 ± 19.76	−3.15 (−17.86 to 11.55)	t = −0.446	0.660
	Week 2, mean ± SD	27.17 ± 11.16	13.78 ± 10.42	13.39 (1.34 to 25.44)	t = 2.402	0.032
	Week 3, mean ± SD	27.63 ± 27.62	10.98 ± 6.85	16.65 (−17.22 to 50.51)	t = 1.308	0.254
	Week 4, mean ± SD	35.58 ± 23.35	23.44 ± 16.61	12.14 (−6.76 to 31.05)	t = 1.361	0.192
Week 4 responder status	Responder (≥50% reduction), n/N (%)	2/10 (20.0%)	0/11 (0.0%)	RD: 20.00 percentage points (−9.79 to 51.74)	Fisher's exact test	0.214
	Non-responder (<50% reduction), n/N (%)	8/10 (80.0%)	11/11 (100.0%)	—		

TABLE 3: Comparison of wound area, percentage wound area reduction, and responder status between groups

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. Independent-samples t-test was used for normally distributed continuous variables, and Mann–Whitney U test was used for non-normally distributed continuous variables. Fisher's exact test was used for categorical variables. A two-sided p-value <0.05 was considered statistically significant. Wound-area analyses were based on participants with available measurements at the respective time points; therefore, denominators may differ from the total randomized sample. For categorical outcomes, risk differences (RD) are expressed in percentage points, calculated as the proportion in the Papaverine group minus the proportion in the Control group, with corresponding 95% confidence intervals (CI). For continuous outcomes, mean differences are reported with 95% CIs.

IQR: interquartile range; SD: standard deviation; t: independent-samples t-test statistic; U: Mann–Whitney U test statistic; RD: risk differences.

At follow-up after the 30-day protocol period, VAC therapy was applied in two participants (13.3%) in the papaverine group and none in the control group, while PolyNovo was applied in 2 (13.3%) and none, respectively (Table 4). Skin and skin-substitute grafting was performed in seven participants (46.7%) in the papaverine group and 2 (14.3%) in the control group. Complete wound healing was documented in 14 participants (93.3%) in the papaverine group and 11 (78.6%) in the control group. Death occurred in none of the papaverine-group participants and in 2 (14.3%) control-group participants. Major below-knee amputation was reported in one participant (6.7%) in the papaverine group and 1 (7.1%) in the control group. The median healing time was 29 days (IQR, 15-88) in the papaverine group and 61 days (IQR, 19-85) in the control group, with no statistically significant between-group difference (P = 0.845).

Variable	Category	Papaverine group (n = 15)	Control group (n = 14)	Effect estimate (95% CI)	Test statistic	p-value
VAC therapy applied	Yes	2 (13.3%)	0 (0%)	RD: 13.33 percentage points	Fisher's exact test	0.483
	No	13 (86.7%)	14 (100%)	—		
PolyNovo applied	Yes	2 (13.3%)	0 (0%)	RD: 13.33 percentage points	Fisher's exact test	0.483
	No	13 (86.7%)	14 (100%)	—		
Skin and skin substitute grafting performed	Yes	7 (46.7%)	2 (14.3%)	RD: 32.38 percentage points	Fisher's exact test	0.109
	No	8 (53.3%)	12 (85.7%)	—		
Complete wound healing	Yes	14 (93.3%)	11 (78.6%)	RD: 14.76 percentage points	Fisher's exact test	0.464
	No	1 (6.7%)	3 (21.4%)	—		
Death	Yes	0 (0%)	2 (14.3%)	RD: −14.29 percentage points	Fisher's exact test	0.224
	No	15 (100%)	12 (85.7%)	—		
Major below-knee amputation	Yes	1 (6.7%)	1 (7.1%)	RD: −0.48 percentage points	Fisher's exact test	1.000
	No	14 (93.3%)	13 (92.9%)	—		
Healing time (days)	Median (IQR)	29 (15–88)	61 (19–85)	HL estimate: −5.15 days (95% CI: −57.00 to 26.00)	U = 85.5	0.845

TABLE 4: Clinical and treatment outcomes during extended follow-up after the 30-day protocol period

Data are presented as median (IQR) or n (%), as appropriate. Fisher's exact test was used for categorical variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. Healing time was calculated as the number of days from the date of the initial/index surgery to the date on which complete wound healing was documented. Because healing-time data were not normally distributed (Shapiro–Wilk test, p = 0.000145), results are presented as median (IQR) and compared between groups using the Mann–Whitney U test. The RD are expressed in percentage points (Papaverine group minus Control group), with corresponding 95% CI. The Hodges–Lehmann estimator was used to estimate the difference in healing time between the groups because healing time was analysed using the non-parametric Mann–Whitney U test. The estimate is expressed in days with a 95% CI. A two-sided p value <0.05 was considered statistically significant.

BK: below-knee; IQR: interquartile range; U: Mann–Whitney U test statistic; RD: Risk difference; CI: Confidence interval; VAC: vacuum-assisted closure.

In the Kaplan-Meier analysis, healthy granulation was achieved in 8 of 15 participants (53.3%) in the papaverine group and 4 of 15 participants (26.7%) in the control group. The remaining 7 (46.7%) and 11 (73.3%) participants, respectively, were censored. The median time to healthy granulation was 29 days (95% CI, 21-NA) in the papaverine group and was not reached in the control group. The groups were compared using the log-rank test ($\chi^2 = 1.60$; P = 0.204) (Tables *5*, *6* and Figure *3*).

Outcome	Papaverine group (n = 15)	Control group (n = 15)	Test statistic	p-value
Healthy granulation achieved, n (%)	8 (53.3%)	4 (26.7%)	—	—
Censored observations, n (%)	7 (46.7%)	11 (73.3%)	—	—
Median time to healthy granulation, days (95% CI)	29 (21–NA)	Not reached	Log-rank χ^2 = 1.60	0.204

TABLE 5: Comparison of time to achievement of healthy granulation between group A and group B

Healthy granulation was analyzed using Kaplan–Meier time-to-event analysis. Participants who had not achieved healthy granulation during the follow-up period were treated as censored observations. The participant who withdrew on postoperative day 5 without achieving healthy granulation was censored at the time of withdrawal. The median time to healthy granulation is presented with the 95% confidence interval (CI); "not reached" indicates that the median could not be estimated because fewer than 50% of participants had experienced the event during follow-up. The two groups were compared using the log-rank test. A two-sided p-value <0.05 was considered statistically significant.

CI: confidence interval; NA: not available.

Group	0 Days	5 Days	10 Days	15 Days	20 Days	25 Days	30 Days
Papaverine group	15	15	11	11	11	10	7
Control group	15	13	12	11	11	10	10

TABLE 6: Number of participants at risk at different time points during follow-up

Numbers represent participants who remained at risk of achieving healthy granulation at each specified time point, according to the Kaplan–Meier analysis. Participants who had already experienced the event or had been censored were no longer included in the risk set.

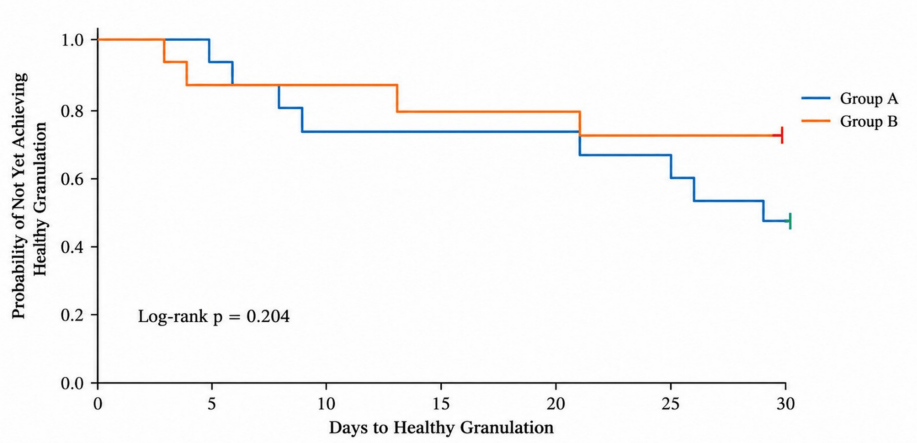


FIGURE 3: Kaplan–Meier curve for time to achievement of healthy granulation

Kaplan–Meier curves showing the probability of not yet achieving healthy granulation over 30 days in the papaverine (Group A) and control (Group B) groups. Healthy granulation was achieved in 8 (53.3%) participants in Group A and 4 (26.7%) participants in Group B. The between-group difference was assessed using the log-rank test (P = 0.204).

Percentage wound-area reduction was assessed at Weeks 1-4 using a linear mixed-effects model. Adjusted mean reductions in the papaverine group were 0.68%, 23.99%, 26.42%, and 34.15%, compared with 3.74%, 13.38%, 12.21%, and 23.35% in the control group, respectively. Between-group comparisons were not statistically significant at any week (Holm-adjusted P = 0.656, 0.240, 0.193, and 0.163, respectively). The overall group effect (P = 0.142) and group × week interaction (P = 0.285) were not significant, while the

overall week effect was significant (P < 0.001) (Table 7).

Follow-up	Papaverine, n (%)	Control, n (%)	Papaverine Adjusted Mean % (95% CI)	Control Adjusted Mean % (95% CI)	Mean Difference % (95% CI)	Holm-adjusted p-value
Week 1	15 (100.0)	12 (80.0)	0.68 (−8.48 to 9.83)	3.74 (−6.44 to 13.91)	−3.06 (−16.75 to 10.60)	0.656
Week 2	8 (53.3)	7 (46.7)	23.99 (11.78 to 36.21)	13.38 (0.33 to 26.44)	10.61 (−7.27 to 28.50)	0.240
Week 3	5 (33.3)	5 (33.3)	26.42 (11.19 to 41.64)	12.21 (−3.05 to 27.47)	14.21 (−7.35 to 35.80)	0.193
Week 4	10 (66.7)	11 (73.3)	34.15 (23.13 to 45.16)	23.35 (12.73 to 33.97)	10.80 (−4.50 to 26.10)	0.163
Overall Group Effect	38/60 (63.3)	35/60 (58.3)	—	—	—	F=2.280; p= 0.142
Overall Week Effect	—	—	—	—	—	F=12.674; p < 0.001
Group × Week Interaction	—	—	—	—	—	F = 1.301; p = 0.285

TABLE 7: Longitudinal comparison of percentage wound-area reduction between papaverine and control groups using a linear mixed-effects model

Data are presented as n (%) or estimated marginal mean (95% CI). Between-group comparisons were performed using estimated marginal means with Holm adjustment. A linear mixed-effects model was used to assess group, time, and group × time effects. A significant time effect was observed (p < 0.001), but the group effect and group × time interaction were not significant.

CI: confidence interval; Holm: Holm–Bonferroni adjustment; F: F-statistic; n: number of available observations.

Discussion

In this randomized, placebo-controlled pilot study of 30 patients with diabetic foot ulcers (DFUs) of ischemic etiology, healthy granulation was achieved in 8/15 (53.3%) participants in the papaverine group and 4/14 (28.6%) evaluable participants in the control group; however, the difference was not statistically significant (P = 0.264). Mean percentage wound-area reduction was 27.17 ± 11.16% versus 13.78 ± 10.42% at Week 2 (P = 0.033), but differences at Weeks 1, 3 and 4 were not statistically significant (Week 4: 35.58 ± 23.35% vs 23.44 ± 16.61%; P = 0.182). The median time to healthy granulation was 29 days (95% CI, 21-not estimable) for papaverine and was not reached for placebo (log-rank P = 0.204). There were no significant differences in VAC use, grafting, general follow-up status, or healing time between groups. This was a small exploratory pilot study, and the results were hypothesis-generating only and do not provide evidence of efficacy [13].

Neuropathy, mechanical stress, infection, and arterial disease are among the common causes of DFU [1]. Only 30-40% will heal by 12 weeks, and treating ischemia is one of the first-line therapies [14]. Guideline-based care involves assessment of the arterial circulation along with debridement, infection control, and offloading [2]. Peripheral arterial disease (PAD) was an independent predictor of non-healing in the EURODIALE cohort (n = 1,088), and the predictors varied between PAD-positive and PAD-negative patients. The results revealed key differences in the factors that predict healing according to PAD status [15]. Our ischemic population, which excluded patients who had undergone angioplasty, was identified using varied clinical or diagnostic criteria. For patients with chronic limb-threatening ischemia, future studies may wish to take into consideration the staging of limb threat using the WIfI classification to standardize and stratify limb threat [16]. When comparing healing proportions in our study with those in EURODIALE, it is important to keep in mind that the proportions may differ because of differences in follow-up, case mix, and care pathways.

The 2023 IWGDF guidance on wound-healing interventions also included some conditional supportive recommendations for certain interventions, and a systematic review revealed low to very low certainty of evidence for most interventions [3, 17].

Adjunctive treatment studies for DFUs can be conducted using placebo-controlled designs. In the TWO2

trial, which was sham-controlled, adjunctive topical oxygen therapy increased healing rates compared with sham treatment [18]. The intervention, population, endpoint, and follow-up were different, however, from those of the present study. Furthermore, in our study, topical oxygen therapy was given to both groups as standard therapy; hence, the separate effect of oxygen therapy on healing could not be distinguished from the effect of papaverine.

The rationale for the use of topical papaverine is based on its ability to inhibit phosphodiesterase and modulate vascular smooth-muscle contraction [4,5] and the use of local papaverine in surgical procedures to improve vascular blood flow [5,6]. Experimental flap studies have yielded better flap survival [7,8]. In a rat skin-flap model, Mahbub et al. reported improved flap survival and increased neovascularization following treatment with papaverine-loaded hydrogel, providing preclinical support for its potential role in compromised tissue perfusion [8]. Impaired angiogenic responses and abnormal vascular remodeling are associated with diabetes during wound repair [19]. A systematic review found that evidence for the use of topical vasodilators in reconstructive microsurgery is still scarce and mostly derived from animal studies that might not be representative of humans [20]. Experimental wound-healing data are also somewhat inconsistent. A single dose of papaverine did not significantly affect bursting pressure, hydroxyproline, neoangiogenesis, or collagen in a rat anastomosis model, but there was some variation in inflammation and necrosis scores on day 7 [21]. The results from flap and vascular-surgical procedures cannot be automatically applied to diabetic foot wounds, and perfusion and mechanisms were not measured in the present study.

A targeted literature search did not identify any previous randomized clinical trial of topical papaverine use in patients with ischemic diabetic foot wounds. The papaverine evidence we came across was experimental or surgical [5,6,8,20,21] and cannot be compared like for like. The present trial extends the randomized, placebo-controlled human dataset, with preliminary estimates of effect, variability, and missing data to inform larger trials [9].

The Week-2 finding ($P = 0.033$) should be interpreted cautiously because it was based on the available measurements and was one of four weekly comparisons conducted without adjustment for multiple testing. In the subsequent longitudinal analysis, the Week-2 difference was no longer statistically significant after Holm adjustment ($P = 0.240$). The overall group effect ($P = 0.142$) and group × week interaction ($P = 0.285$) were also not significant, while the effect of week was significant ($P < 0.001$). This indicates that wound-area reduction changed over time, but the analysis did not show a significant difference in the pattern of change between the groups. The Week-4 responder analysis included 10 participants in the papaverine group and 11 in the control group. Absolute wound areas did not differ between groups at any time point (all $P \geqslant 0.833$), and the differences in percentage wound-area reduction at Weeks 3 and 4 were also not statistically significant. These findings are consistent with reports from studies of venous leg ulcers and diabetic foot ulcers, in which greater early wound-area reduction has been associated with subsequent wound closure [22]. They also highlight the value of standardized early wound measurements in future trials. However, the Week-2 finding should not be considered evidence of a confirmed treatment effect. The Kaplan-Meier analysis was also imprecise: the median time to healthy granulation was not reached in the control group, and the between-group difference was not significant (log-rank $P = 0.204$). As recommended for pilot studies, estimates and their uncertainty should be considered alongside statistical significance [23]. A numerical difference does not establish treatment benefit, just as a non-significant result does not establish equivalence between groups.

The longitudinal analysis of percentage wound-area reduction using a linear mixed-effects model provides a more comprehensive assessment of changes over time. A significant overall effect of week was observed ($P < 0.001$), indicating that wound-area reduction changed during follow-up. However, neither the overall group effect ($P = 0.142$) nor the group × week interaction ($P = 0.285$) was statistically significant, indicating that the longitudinal pattern of wound-area reduction did not differ significantly between the papaverine and control groups. Furthermore, none of the between-group comparisons at individual follow-up weeks remained statistically significant after Holm adjustment, including the Week-2 comparison ($P = 0.240$). These findings do not establish a treatment effect of papaverine on wound-area reduction and should be interpreted cautiously given the small sample size and incomplete wound-area measurements.

Clinical outcomes were not clear-cut. Within one month, VAC therapy was used in 5 (33.3%) participants in the papaverine group and 3 (21.4%) in the control group, while grafting was performed in 2 (13.3%) and none, respectively. During extended follow-up after the 30-day protocol period, skin and skin-substitute grafting was documented in 7 (46.7%) participants in the papaverine group and 2 (14.3%) in the control group. Complete wound healing was documented in 14 (93.3%) participants in the papaverine group and 11 (78.6%) in the control group; however, this difference was not statistically significant ($P = 0.464$). The median time to complete wound healing was numerically shorter in the papaverine group (29 days [IQR, 15-88]) than in the control group (61 days [IQR, 19-85]), although the between-group difference was not statistically significant ($P = 0.845$). After the 30-day protocol period, VAC therapy and PolyNovo application were each reported in 2 (13.3%) participants in the papaverine group and none in the control group. Two deaths were recorded in the control group and none in the papaverine group, while major below-knee amputation occurred in one participant in each group. No study-related adverse events (AEs) or serious adverse events (SAEs) were reported; nevertheless, safety conclusions are limited by the small sample size. The numerical differences in healing outcomes do not establish a treatment effect, and no inference

regarding mortality or amputation can be made because the study was not powered to evaluate these outcomes. Overall, these findings should be interpreted cautiously given the small sample size and exploratory nature of the study.

Although wound-area reduction provides a clinically relevant indication of wound progression, the observed changes should be interpreted as exploratory findings in this pilot study. They do not establish a definitive treatment effect of topical papaverine, and confirmation in adequately powered, multicentre randomized controlled trials with standardized wound measurements and follow-up is warranted.

Strengths include a computer-generated randomization sequence, concealed allocation (sealed, opaque, sequentially numbered envelopes), a placebo applied using an identical procedure, blinding of participants, the investigator and outcome assessor through coded syringes, prospective registration (CTRI/2025/01/079660), no post-commencement protocol changes, and a clinically relevant ischemic population.

Several limitations should be considered when interpreting these findings. First, the study included a small, single-centre sample recruited by purposive sampling, which limits the precision and generalizability of the findings. Wound-area measurements were incomplete and obtained at irregular intervals, and one participant in the control group withdrew on postoperative day 5. The primary follow-up period was limited to 30 days. In addition, healthy granulation was used as the primary outcome and was defined by wound colour and reduction in wound size; as a surrogate outcome, its clinical relevance depends on its ability to reliably predict clinically meaningful outcomes such as complete wound healing [19]. The criteria used to define ischemia were also heterogeneous, potentially introducing variability in the study population. Concomitant and subsequent wound-care interventions, including debridement, topical oxygen, vasoactive medications, VAC therapy, and grafting, may have influenced healing independently of the study intervention. Although several baseline characteristics differed numerically between groups, including multiple ulcers, osteomyelitis, and CRP levels, the small sample size limits the ability to exclude clinically relevant baseline imbalance. Finally, the wound-area analyses were exploratory and were further limited by incomplete measurements and varying assessment times. The wound-area analyses involved repeated comparisons across multiple time points without adjustment for multiplicity, increasing the possibility of a chance finding.

Conclusions

In this pilot randomized controlled study, topical papaverine was associated with a numerical difference in wound-area reduction at Week 2 in the earlier exploratory analysis; however, this finding was not supported by the Holm-adjusted longitudinal analysis, and no statistically significant group × week interaction was observed. No statistically significant between-group difference was observed in the primary outcome of healthy granulation at the end of the 30-day protocol period or in other evaluated clinical healing outcomes. No study-related adverse events or serious adverse events were reported during the protocol-defined study period. These findings do not provide sufficient evidence to establish the efficacy of topical papaverine for ischemic diabetic foot wounds but may inform further investigation of this approach. Larger, adequately powered randomized controlled trials with standardized wound assessment and prespecified analysis plans are warranted to determine whether topical papaverine provides a clinically meaningful benefit.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Mahalaxmi Healthcare Pvt. Ltd. Institutional Ethics Committee (MHPLIEC) issued approval ECR/1959/Inst/MH/2024. The study received Institutional Ethics Committee approval on 28 December 2024. Written informed consent was obtained from all participants before enrollment. Informed consent forms and source documents were retained at the study site. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance

with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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