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Comparative Study Between Silver Nanoparticles Dressing (SilvrSTAT Gel) and Conventional Dressing in Diabetic Foot Ulcer Healing: A Prospective Randomized Study

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Abstract

Background. We are trying to evaluate silver nanoparticles' effectiveness (SilvrSTAT Gel) in accelerating healing rate of nonischemic diabetic foot ulcers (DFUs). *Methods*. This prospective, double-blind, randomized, controlled study includes 80 patients with nonischemic DFUs classified into 2 groups. Group A was subjected to SilvrSTAT Gel dressing, and group B was subjected to conventional dressing (wet-to-moist dressing with or without povidone-iodine). All cases had minimal debridement before treatment. In both groups, all cases were nonischemic after successful revascularization either by bypass surgery or endovascular therapy. *Results*. The healing rate of the SilvrSTAT group was significantly higher than that of the conventional group. The healing rate per week of the SilvrSTAT group was considerably higher than that of the conventional group ($P < .0001$). The rate of complete healing for ulcers in group A was achieved in 22 patients (55%) by the 6th week, while 29 (72.5%), 34 (85%), and 36 (90%) patients were healed entirely by the 8th, 10th, and 12th weeks, respectively. In group B: 20 (50%), 27 (67.5%), and 30 (75%) patients were completeley healed by the 8th, 10th, and 12th weeks, respectively. *Conclusions*. SilvrSTATGel is effective in the treatment of DFU.

Keywords

foot ulcer, SilvrSTAT Gel, nanoparticles, conventional dressing, healing

Introduction

Diabetic foot ulceration is an unavoidable sequela of diabetes mellitus (DM) during many patients' clinical course. Up to 25% of diabetic patients will suffer from a foot ulcer during their lifetime. Approximately 20% of these ulcers require amputation, and 85% of all diabetic lower extremity amputations are preceded by an ulcer.[1] Unfortunately, these patients are 15 to 30 times more likely to undergo an amputation than those without DM.[2]

The use of silver was neglected when penicillin and other antibiotics were developed. With the appearance of antibiotic-resistant bacteria and silver's low tendency to create resistant strains, significant attention to silver has regained.[3]

Silver nanoparticles (AgNPs) have broad-spectrum antimicrobial activity because of a multisite action and intrinsic therapeutic characteristics. AgNPs have demonstrated several rules in different applications, such as the delivery of drugs, biomaterials, and device coating, for antibacterial agents, diagnosis, and detection in addition to regeneration materials. Recently, the antibacterial properties of AgNPs have led to increasing its rule in medical implementations such as dressings of a wound, anti-neoplastic drug carriers, and artificial implantation.[4-8]

There are several mechanisms by which AgNPs can destroy the bacteria. They include bacterial membrane destruction, the crossing of the microbial body and initiation of intracellular destruction, removal of lipopolysaccharide with cellular disintegration, the induction of oxidative stress, and metal release ions in addition to nonoxidative stress mechanisms.[6,9,10] This study aimed to evaluate the efficacy and healing rate of silver nanoparticles (SilvrSTAT Gel) in diabetic foot ulcers (DFUs) healing.

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Patients and Methods

Study Design

This is a single-centered, prospective, double-blind, randomized, controlled study that was conducted at the General Surgery Department of Benha University Hospital between September 2017 and March 2020.

Inclusion Criteria

1. Type 1 or 2 DM on either oral hypoglycemic or insulin therapy
2. Presence of revascularized nonischemic DFUs after successful bypass surgery or endovascular intervention
3. Presence of a foot ulcer for at least 6 weeks duration
4. No clinical evidence of infection at the ulcers site
5. Wagner type I or II ulcers

Exclusion Criteria

1. Wagner type III, IV, and V ulcers
2. Peripheral artery disease (PAD)
3. Clinical signs of infection
4. Presence of gangrene in the ulcer or any part of the foot
5. Patients with a history of suspected osteomyelitis
6. Surface area of ulcer <2 cm^2
7. Exposure of bone, tendon, and ligament at ulcer bed
8. Patients with a history of radiation or chemotherapy within 3 months of randomization
9. Low serum albumin (<3 g/dL)
10. History of silver hypersensitivity
11. Patients on renal dialysis, immunocompromised, history of liver, hematological, nutritional, collagen, and vascular diseases
12. Patients with active cancer

After the approval of the study by the ethical committee of the Faculty of Medicine, Benha University, and after obtaining written informed consent from the patients on the 2 methods of dressing and their benefits, risks, other options of management, and possible complications, this prospective randomized controlled study was carried out on 80 patients with a nonischemic, noninfected, nonhealed DFU. The patients were randomly assigned into 2 groups: group A, which received silver nanoparticles (SilvrSTAT Gel) dressing (N = 40), and group B, which received conventional dressing (wet-to-moist dressing with or without povidone iodine) in addition to offloading for planter site ulcers. The sample size of the study was calculated using online software (https://clincalc.com/stats/samplesize.aspx).

Based on the study's primary endpoint (reduction in the ulcer surface area) and in light of previous literature,[11-13] no patient was withdrawn from the study after randomization in addition to no changes to methods and outcomes after the commencement of the trial (Figure 1).

Methods of Randomization and Blinding

A Microsoft Excel sheet was used to create a randomization sequence with a 1:1 allocation using random block sizes of 2 and 4 by an independent doctor. Each eligible patient was subjected to 1 of the 2 dressing groups: SilvrSTAT Gel group or conventional dressing group. Patients received the next available successive randomization number and dressing type based on the randomization schedule. The first surgeon (blind one) selected the eligible patients, prepared ulcers by excision debris and necrotic tissue, documented the site, length, width, depth, and grades of the ulcers, and was responsible for the follow-up of the ulcers during outpatient clinic visits with documentation of the size of the ulcers. The first surgeon was blind to dressing type. The second participating surgeon (unblind one) knew the number of the patients and each patient's group according to a randomization schedule electronically generated. He also knew the type of dressing used and prepared dressings for the patients.

Eligible Cases

1. SilvrSTAT Gel group (40 patients): in this group SilvrSTAT Gel applied to the ulcers.
2. Conventional dressing (40 patients): in this group, wet-to-moist dressing with or without povidone-iodine was applied to the ulcers.

All patients with nonhealing feet ulcers were subjected to full vascular assessment including arterial and venous duplex, laboratory investigations, X-ray foot, ulcer assessment including size and site, and initial photos as a baseline with follow-up photos. All patients with plantar ulcers were subjected to offloading by use shoe orthoses.

Surgical Intervention

Surgical debridement of the ulcers was done in both groups to refresh the ulcer bed and remove all necrotic tissue and debris. The sites, ulcer's dimensions (length, width, and depth), and grade of the ulcers were reported.

Protocols of Dressing

Group A. SilvrSTAT Gel was applied directly to the ulcer after cleaning with a surgical soap solution then covered with a conventional dressing. The frequency of dressing change was every 72 hours. The dressing was done for up to

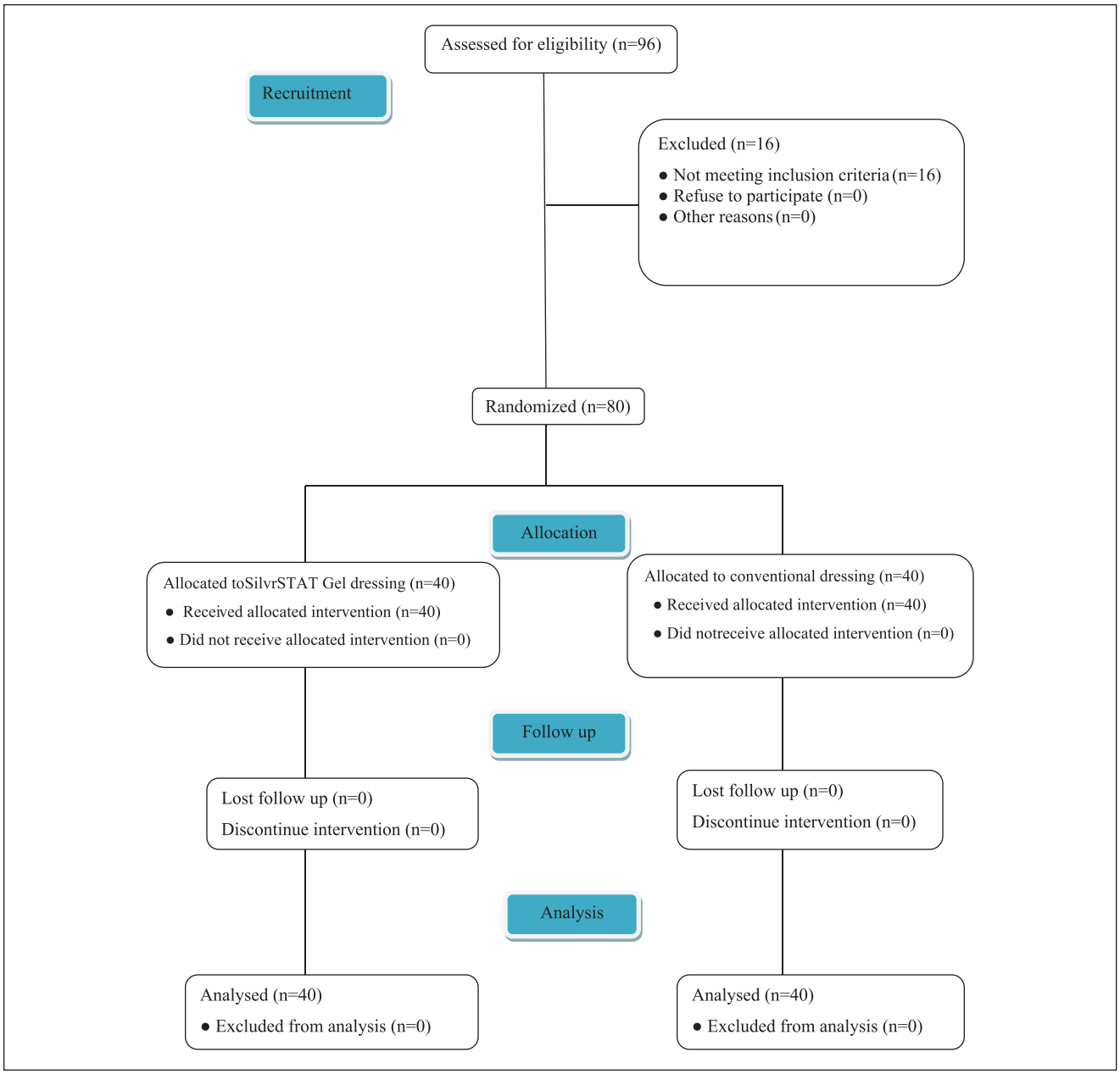

Figure 1. CONSORT flowchart demonstrating patient recruitment and exclusion.

12 weeks or stopped if the ulcer healed.

Group B. Wet gauze pads or packing tape was applied on the ulcer with a careful filling of the ulcer and any cavity under the skin followed by covering with wet gauze or tape and a large dry dressing pad. The frequency of the dressing change was daily.

Follow-up

All patients were instructed to visit our clinic at scheduled sessions twice weekly for a maximum follow-up period of 12 weeks. Clinical outcome evaluation included assessing the rate of ulcer's healing by measuring ulcer's dimensions (length, width, and depth) with calculation of surface area and volume. Follow-up photos were taken. All patients underwent full laboratory investigations every 4 weeks until target endpoint.

Endpoints

Primary Endpoints. Reduction in the wound size by calculating the surface area and volume of the ulcers every week during follow-up period. Surface area was calculated using

Mayrovitz formula (A [area] = L [length] × W [width] × 0.785), while volume was calculated using *Kundin* formula (V [volume] = A × D [depth] × 0.327).[14,15] Healing area was calculated by subtraction of the ulcer's remaining surface area from each other, for example, subtraction of the surface area of the ulcer in the second week from surface area in the first week.

Secondary Endpoints. Rate of complete healing during follow-up period.

Statistical Analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS) (version 16; SPSS Inc). Quantitative data were presented as mean ± standard deviation (SD) and were analyzed using a one-way unpaired *t* test to compare quantitative variables as parametric data (SD <50% mean). Qualitative data were presented as numbers and percentages and were analyzed using χ^2 and Fisher's exact tests. A *P* value of <.05 was considered significant, whereas a *P* value of <.01 was considered highly significant. However, a *P* value of >.05 was considered insignificant.

Results

This prospective, double-blind, randomized, controlled study includes 80 patients with DFUs who met the inclusion criteria between September 2017 and March 2020. There is no statistically significant variation regarding demographic data, laboratory data, DM-related complications, antidiabetic medications, DM, and Ankle Branch Index duration. There was no statistically significant variations in the site of ulcers ($P = 0.67$). In group A, most of the ulcer sizes (33 out of 40) ≤7.6 cm^2 in area and ≤2 cm^3 in volume, only 7 cases had surface areas >7.6 cm^2 and a volume >2 cm^3. In group B, most ulcer sizes (35 out of 40) were ≤7.3 cm^2 in area and ≤2 cm^3 in volume with only 5 cases having surface areas >7.3 cm^2 and volume >2 cm^3. There were no statistically significant variations between both groups regarding ulcer dimensions. No adverse events were reported in each intervention group. No side effects, pain, or irritation has been reported in nanoparticles group. The baseline features of both groups are summarized in Table 1.

Primary Outcome

The ulcer healing rate in group A was significantly faster than group B. There was a statistically significant difference between group A and B regarding the ulcer healing rate per week. Healing area over time is summarized in Table 2.

Secondary Outcome

There was a statistically significant difference between group A and group B regarding the rate of completely healed ulcer at 8th, 10th, and 12th weeks ($P < .001$; Figure 2).

The rate of complete healing is summarized in Table 3.

Analysis of the Factors Associated With Complete Healing of the Ulcer

A univariate and multivariate analysis of the factors associated with complete healing of DFUs was done. There were no statistically significant differences regarding age, sex, site, duration, comorbidities, surface area, and volume of the ulcers between completely healed and nonhealed ulcers (Tables 4 and 5).

Discussion

Diabetic foot ulcers are a major socioeconomic and health problem associated with patients' psychological impact. Unfortunately, more than 85% of major nontraumatic lower-limb amputations are preceded by DFUs, representing a 15 times higher rate than in non-diabetics. Two to three percent of diabetic patients will develop DFUs each year and a lifetime risk of developing DFUs of 15%.[2]

There is a definite consensus regarding the definition of acute and chronic ulcers. Most authors agree that an acute ulcer should heal in less than a month, while in most cases, a chronic ulcer has duration of 6 months or more.[16]

Wound healing is a complex multidiscipline harmony process. Several factors affect wound healing; these factors are systemic and local. Systemic factors are DM, PAD, systemic vacuities, physical pressure, and aging. Local factors are local bacterial colonization, high inflammatory cytokines, low concentration of beneficial cytokines, and derangement of matrix metalloproteinase. All these factors create a vicious cycle that results in the prolongation of the process of wound healing. During the management of such wounds, all these factors should be considered for successful results.[17]

Some ulcers may remain not responsive to the usual standard treatment, such as debridement, dressings, and even skin grafting. These methods are incapable of supporting ulcers with growth factors needed to enhance wound healing process.[18] There are several novel wound management modalities like negative pressure wound therapy, growth factor products, maggot therapy, hyperbaric oxygen therapy, and bioengineered tissue or skin substitutes to aid in the wound healing process.[19] One of these modalities is silver nanoparticles (SilvrSTAT Gel).

Table 1. Patient Characteristics in Both groups.

Parameters		Group A (N = 40)	Group B (N = 40)	*P*
Age, mean ± SD (range)		55.8 ± 2.38 (52-60)	54.64 ± 3.54 (50-60)	.67
Sex	Male	26 (65%)	14 (40%)	.57
	Female	28 (70%)	12 (30%)	.54
Insulin therapy		9 (22.5%)	11 (27.5%)	.49
Oral hypoglycemic medications		31 (77.5%)	29 (72.5%)	.78
HbA1c		7.1-8.6 (6.7 ± 1.1)	7.5-8.8 (6.9 ± 1.5)	.36
Hemoglobin (mg/dL)		11-13.5 (10.5 ± 2.7)	12-15.2 (11.3 ± 3.2)	.68
Albumin (g/dL)		4.4-5.2 (4.5 ± 1.2)	4.3-4.9 (4.1 ± 1.1)	.35
Duration of DM (years), range (mean ± SD)		7-11.5 (10.2 ± 2.1)	6-10.5 (8.2 ± 2.3)	.77
Hypertension		14 (35%)	16 (40%)	.76
Nephropathy		8 (20%)	5 (12.5%)	.75
Stroke and ischemic heart disease		4 (10%)	6 (15%)	.64
Retinopathy		9 (22.5%)	10 (25%)	.69
Smoking		15 (37.5%)	12 (30%)	.72
Bypass surgery		4 (10%)	6(15%)	.54
PTA ± stenting		32 (80%)	38 (95%)	.68
ABPI		0.8 ± 0.14	0.83 ± 0.12	.47
Sites of ulcers	Dorsum mid-foot	9	5	.58
	Dorsum fore foot	9	15	.98
	Planter hind foot	5	3	.73
	Planter fore foot	4	2	.91
	Planter mid-foot	13	15	.63
Surface area of the ulcers (cm^2), mean ± SD		7.8 ± 1.3	7.21 ± 1.16	.57
Volume of the ulcers (cm^3), mean ± SD		1.952 ± 0.67	1.91 ± 0.38	.63

Abbreviations: SD, standard deviation; HbA1c, glycosylated hemoglobin; DM, diabetes mellitus; PTA, percutaneous transluminal angioplasty; ABPI, ankle brachial pressure index.

Table 2. Healing Area Over Time in Both Groups.

Time	Group A (N = 40)	Group B (N = 40)	*P*
Second week	1.4 ± 0.008	0.82 ± 0.08	<.0001
Fourth week	2.65 ± 0.037	1.97 ± 0.06	<.0001
Sixth week	3.78 ± 0.17	2.83 ± 0.0.07	<.0001
Eighth week	5.24 ± 0.09	3.88 ± 0.05	<.0001
10th week	6.4986 ± 0.06	4.72 ± 0.09	<.0001
12th week	7.7 ± 0.01	5.77 ± 0.12	<.0001
Ulcer healing rate per week	0.68 ± 0.07	0.47 ± 0.04	<.0001

Silver nanoparticles have antibacterial and anti-inflammatory effects and improve the healing of the ulcers and wounds. Nanosilver (NS) has broad and potent antibacterial activity because of the multifaceted mechanisms by which NS acts on bacteria. These mechanisms include the interaction of silver ions with the plasma membrane and peptidoglycan of the cell wall, resulting in lysis of cell membrane and cytoplasmic DNA, prevention of replication of DNA, and protein synthesis. Furthermore, NS can directly damage the plasma membrane and cell wall.[20-25] Revelli et al reported a comparative study between silver nanoparticles' antibacterial efficacy in the form of silver Sol (ASAP solution) and 5 classes of antibiotics (penicillins, macrolides, cephalosporins, tetracyclines, and quinolones). He documented that silver Sol was found to have a broad-spectrum antimicrobial activity than the other antibiotics.[26]

Silver hydrogel (SilvrSTAT Gel) contains Ag0 nanoparticles at 32 parts per million. It has several indications, such as dressing for DFUs, pressure ulcers, surgical site infection, autograft and allograft sites, first- and second-degree burns, chronic venous ulcers, lacerations, and abrasions, wounds for an inserted device, and donor sites. The efficacy of a dressing containing silver nanoparticles has been widely examined in vitro. Recent research has shown that these types of dressings have a rapid, potent, and broad-spectrum antimicrobial activity against Gram-positive and harmful bacteria.[27-30]

Figure 2. Case from group A: (A) after debridement, (B) after 2 weeks, (C) after 4 weeks, and (D) after 8 weeks.

Table 3. Rate of Complete Healing of the Ulcers Over Time.

Time	Group A (N = 40), n (%)	Group B (N = 40), n (%)	*P*
Second week	0	0	
Fourth week	0	0	
Sixth week	22 (55%)	0	1.000
Eighth week	29 (72.5%)	20 (50%)	<.001
10th week	34 (85%)	27 (67.5%)	<.001
12th week	36 (90%)	31 (77.5%)	<.001

Table 4. Clinical Variables of Patients With Complete Healing Versus Patients Without Healing.

Clinical and laboratory variables		Completely healed group, N = 67	Nonhealed or partially healed group, N = 13	*P*
Age (years)		53.8 ± 2.6	56.7 ± 4.5	.217
Sex (male/female)		35/32	8/5	.891
Mean duration of ulcer (months)		5.2 ± 1.6	6.1 ± 2.27	.76
Site of ulcer	Dorsum (mid and forefoot), n (%)	33 (49.2%)	5 (38.5%)	.139
	Planter (mid and forefoot), n (%)	28 (41.8%)	6 (46.2%)	.342
	Planter hind foot (heal), n (%)	6 (8.95%)	2 (15.4%)	.382
Size of the ulcer	Surface area	6.9 ± 2.3	7.11 ± 1.03	.321
	Volume	1.67 ± 0.57	1.82 ± 0.49	.293
Mean HbA1c before treatment		7.9 ± 1.1	8.6 ± 0.7	.413
Mean HbA1c at 12 weeks		7.1 ± 0.82	7.5 ± 0.9	.671
Comorbidities, n (%)		40 (59.7%)	9 (69.2%)	.253

Abbreviation: HbA1c, glycosylated hemoglobin.

In the current study, the rate of completely healed ulcer in the SilvrSTAT group was statistically significantly higher than the conventional group at eighth, 10th, and at 12th weeks (29 [72.5%] vs 20 [50%], 34 [85%] vs 27 [67.5%], 38 [90%] vs 31 [77.5%]), respectively, in addition to a statistically significant difference between 2 groups regarding healing rate over time ($P < .0001$).

Only a few studies have investigated the efficacy of SilvrSTAT Gel dressing in DFU and surgical site. Lullove et al reported a case series that included 15 patients with advanced comorbidities such as PAD and demonstrated the efficacy of SilvrSTAT Gel in DFUs and surgical site. The average healing rate in patients with DFUs was 36.75 ± 20.38 days. The surgical site patients showed an average

Table 5. Factors Associated With Complete Healing of DFU.

Variables			Odds ratio	95% CI
Univariate	Age <56 years		0.531	0.266-1.008
	Male		0.503	00263-0.874
	Site of the ulcer	Dorsal (mid and forefoot) ulcers	0.571	0.251-1.096
		Planter (mid and forefoot) ulcers	0.499	0.211-1.043
		Planter hind foot (heal) ulcers	0.512	0.173-0.927
	Surface area <7 cm^2		0.462	0.342-0.759
	Volume <1.8 cm^3		0.422	0.551-0.741
	HbA1c <8		0.359	0.438-0.871
Multivariate	Age <56 years		0.642	0.352-1.083
	Surface area <7 cm^2		0.663	0.357-0.767
	HbA1c <8		0.721	0.554-0.962

Abbreviations: DFU, diabetic foot ulcer; CI, confidence interval; HbA1c, glycosylated hemoglobin.

healing rate of 31.75 ± 16.04 days.[31] Almonaci et al reported 2 cases with DFUs who underwent dressing with silver nanoparticles (AgNPs solution), a significant improvement in the evolution of ulcers was noted on AgNPs administration. The edges of the ulcers reached the point of closure.[32]

Finally, SilvrSTAT Gel dressing is a useful dressing in DFU healing. Limitations of the study can be attributed to a lack of standardization of the frequency of application. Whether the silver dressing was applied once or twice a week or depending on the ulcer status after clinical assessment, one cannot reach a secure protocol regarding the use of this novel technique. Extra-randomized, blinded controlled studies are needed to help quantify the effectiveness of this technique. Furthermore, analysis of the microorganism type associated with DFU is required.

Conclusion

SilvrSTAT Gel is a novel modality in the treatment of DFU that can accelerate wound healing compared with other conventional treatment modalities.

Authors' Note

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Mohamed S. Essa: study conception, design, analysis and interpretation of data, and drafting of manuscript.
Khaled S. Ahmad: drafting of manuscript and critical revision of manuscript.
Mohamed E. Zayed: acquisition of data, analysis, and interpretation of data.
Samia G. Ibrahim: drafting of manuscript and critical revision of manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This data collection were approved by the Ethical Committee of Benha Faculty of Medicine (No. RC.1.3.2020).

Informed Consent

Informed consent was obtained from all individual participants included in the study. Written consent was obtained for publication of this study.

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Trial Registration

Trial registered in the Thai Clinical Trials Registry (TCTR20200630002), registered on June 23, 2020.

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