Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Collagen dressing in the treatment of diabetic foot ulcer: A prospective, randomized, placebo-controlled, single-center study

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ARTICLE INFO

Article history:
Received 21 April 2019
Received in revised form
16 July 2019
Accepted 13 September 2019
Available online 16 September 2019

Keywords:
Diabetic foot ulcer
Wound healing
Collagen dressing

ABSTRACT

Aims: Because collagen is fundamental to wound healing and skin formation, collagen-containing dressing materials might be beneficial in treating diabetic foot ulcers (DFU), but supporting evidence is needed. Here, we examined the effectiveness and safety of collagen dressing material in DFU treatment.

Methods: This prospective, randomized, placebo-controlled, single-center study included patients with type 1 or 2 diabetes and palpable foot pulse who had Wagner grade 1 or 2 ulcers $\geq$1.0 cm^2 with no signs of healing for $\geq$6 weeks. Patients were treated with foam dressing alone (control group) or with a porcine type I collagen dressing material (collagen group). Complete ulcer healing rate was the primary endpoint, and healing velocity and time to 50% size reduction were secondary endpoints.

Results: Thirty patients were included (collagen group: 17, control group: 13). There were no significant differences in demographic factors or baseline DFU characteristics. Compared to the control group, the collagen group presented a higher rate of complete healing [82.4% vs. 38.5%, $P = .022$], faster healing velocity ($P < .05$), and shorter median time to 50% size reduction (21 versus 42 days; hazard ratio = 1.94, $P < .05$).

Conclusions: Wound management using collagen materials in DFUs showed faster and complete healing rate.

1. Introduction

Neuropathy or angiopathy caused by diabetes mellitus may lead to foot ulceration [1,2]. The lifetime risk of diabetic foot ulcer (DFU) in diabetic patients is as high as 25% [3]. DFU is the leading cause of lower leg amputation in diabetic patients, and in 85% of the amputation cases, surgery is performed to address DFU progression [4,5]. After an amputation, ~30% of patients lose their contralateral limb within 3 years [6]. However, it is difficult in clinical practice due to several limitations including neuropathy, angiopathy, concomitant infection, and impaired process of wound healing in diabetic patients. Various dressing materials have been developed to overcome these factors and are currently under clinical trials [7].

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https://doi.org/10.1016/j.diabres.2019.107861
0168-8227/

Collagen is an essential element of the human body as a major component of the extracellular matrix. It provides muscular strength and flexibility and affects connective tissue tensile strength. Collagen is also a major fibrous protein that forms skin, bones, tendons, cartilages, vessels, and teeth. It is widely used as a medical device due to its simple structure and manageability [8].

In 1970, topically applicable microcrystalline collagen was produced from bovine skin [9], and the collagen material was first used as a hemostatic agent [10,11]. Nowadays, different types of dressing materials that contain collagen fiber, collagen membrane, collagen gel, or collagen sponge are used in various medical settings [12–16]. Due to its hemostatic effect and low antigenicity, implanted collagen survival rates are ~80–100% in animal studies, and the materials remain stable until several weeks after surgery with low inflammatory responses or foreign body reaction. Based on promising results, collagen has been successfully used in biocompatible dressing materials for various wounds such as burns or ulcers [17]. Burton reported the use of collagen sponges for foot ulcer management [18]. Recent studies described the effect of a collagen matrix made from types I and III collagen in oral cavity soft tissue defects, which facilitated re-epithelialization and decreased contraction [19]. Most studies on collagen dressing materials have evaluated collagen products mixed with other materials. Few have reported the effect of collagen dressing materials on DFUs [20–22]. This study aimed to identify the clinical effectiveness and the safety of 100% porcine type I collagen dressing material in patients with DFU.

2. Methods

2.1. Patients and study design

This study was a prospective, randomized, placebo-controlled, single-center study. From November 2011 to September 2014, diabetic patients with foot ulcers were consecutively recruited in an outpatient clinic. The clinical study protocol and informed consent process were approved by the Institutional Review Board prior to study initiation.

Patients were eligible for study inclusion if they met the following criteria: type 1 or 2 diabetes mellitus; DFU size $\geq$1.0 cm^2; ulcer persisting for >6 weeks without any sign of healing; Wagner ulcer grade 1 or 2; and adequate distal extremity arterial flow, defined as either transcutaneous partial pressure of oxygen ($TcPO_2$) $\geq$30 mm Hg or palpable pulses at either the dorsalis pedis artery or posterior tibial artery of the ankle. Patients were excluded if they had any infection, osteomyelitis, or other disorder that could interfere with wound healing such as deep venous thrombosis, rheumatoid arthritis, systemic lupus erythematosus, or any other systemic inflammatory disease. Patients were also excluded if they were pregnant or being treated with corticosteroids, immunosuppressive drugs, or chemotherapy. Other conditions for which patients were excluded were the presence of any systemic wasting disease (e.g., chronic obstructive pulmonary disease, sickle cell disease, chronic heart failure, or malignant tumor), Charcot arthropathy of the foot, or severe malnutrition (defined as serum albumin <3.0 g/dL). Patients were excluded if they had prior or ongoing treatments with growth factors or bioengineered tissue products in the past 14 days.

Eligible patients were identified based on physical examination and review of medical records at a screening visit, and eligibility was further assessed based on general laboratory tests (complete blood count, serum chemistry screen, and urinary analysis). After informed consent for participation was obtained by the clinical research coordinator, enrolled patients were randomized to the two study groups in a 1:1 ratio. The randomization code was generated using a permuted-block method with a block size of four or six implemented using the SAS system (Version 9.2, SAS Inc., Cary, NC, USA). Randomization was stratified by clinical center. This trial was registered with the Clinical Research Information Service (KCT0003802, https://cris.nih.go.kr).

2.2. DFU evaluation and wound care procedures

Prior to wound assessment and before each collagen dressing application, DFUs were thoroughly cleaned with saline solution to remove debris and necrotic tissue and expose healthy tissue. Patients in the collagen group were treated with a 100% porcine type I collagen sheet (SK bioland Co., Ltd., Cheongju, South Korea, Figs. 1 and 2) covered by a polyurethane foam dressing (Allevyn, Smith & Nephew, Hull, United Kingdom), while patients in the control group were treated with only polyurethane foam dressing (Allevyn). Dressing changes were performed two or three times per week. All patients were ambulatory, and offloading devices used were preapproved by the clinical research coordinators and selected by the investigators at patient enrolment. Patients were instructed that it was important to always wear the offloading device. Initial DFU evaluation included ulcer size measurement, microbial culture, DFU description, and clinical photography. DFU size was measured using a Digital

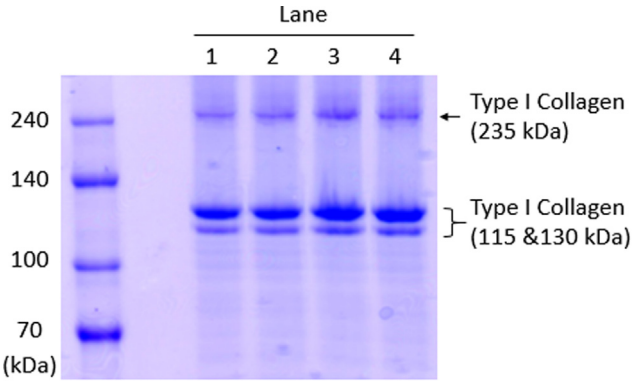

Fig. 1 – Sodium dodecyl sulfate polyacrylamide gel electrophoresis showing similar band patterns and high purities of type I collagen dressing material. Lane 1: control sample 1 (type I collagen from Sigma, St. Louis, MO, USA). Lane 2: control sample 2 (type I collagen from Sigma). Lane 3: injectable type I collagen (from Koken, Tokyo, Japan). Lane 4: 100% type I collagen dressing material in this study (from SK bioland).

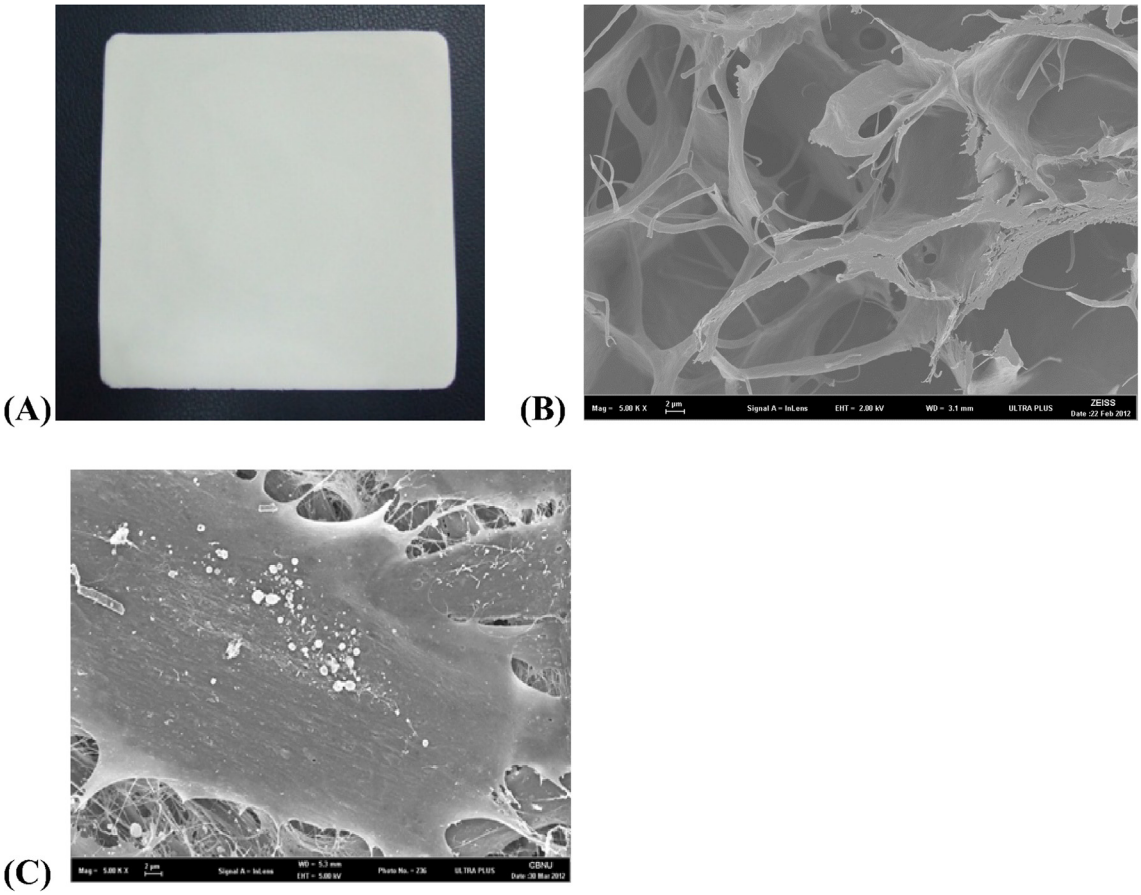

Fig. 2 – Images of 100% collagen dressing material. (A) Photograph of a 10 × 10-cm collagen sheet, (B) scanning electron microscope image (×5000) of the material, (C) scanning electron microscope image (×5000) of fibroblasts cultured on the material to demonstrate biocompatibility.

Planimetry Wound Measurement System (Visitrak®, Smith & Nephew). Clinical staff performing DFU evaluations were blinded to study group allocation. Ulcers were evaluated weekly until complete healing or for up to 12 weeks if complete healing was not achieved. Adverse events, laboratory assessments, and vital signs were monitored using a standardized protocol.

2.3. *Primary and secondary endpoints*

The primary endpoint was the complete healing rate within the 12-week study (Fig. 3). Complete healing was defined as complete re-epithelialization of the ulcer bed and an absence of discharge. Secondary endpoints included DFU healing velocity, which was calculated as the size or percent reduction in the DFU area per week, and the median time to achieve 50% size reduction, which was estimated using Kaplan-Meier survival analysis.

2.4. *Statistical analyses*

All analyses were conducted according to the intention-to-treat principle. Statistical comparisons for continuous variables (e.g., DFU size and healing velocity) were performed with Wilcoxon rank-sum tests. Chi-squared tests or Fisher's exact tests were conducted to compare categorical data measurements between groups. A Kaplan-Meier survival analysis with log-rank testing was performed to evaluate the median time to 50% size reduction and median time to complete healing. A P value <0.05 was considered statistically significant. All statistical analyses were performed by an independent statistician using the SAS system.

3. Results

3.1. *Patient Demographics and baseline characteristics*

All individuals in an initial cohort of potential subjects (n = 39) met the inclusion criteria. Among these 39 participants, 19 and 20 were assigned to the collagen and control groups, respectively. Overall, 30 (76.9%) patients completed the trial and 9 patients did not due to protocol violations including taking a prohibited drug, operation at another site, diagnosis of cancer, and loss to follow-up (Fig. 4). Thirty patients were included in the final analysis (collagen group: 17 patients, control group: 13 patients).

Demographic characteristics, medical status at the screening visit, and baseline DFU characteristics are presented in Table 1. Demographic factors including age, gender, and body mass index did not differ significantly between the two

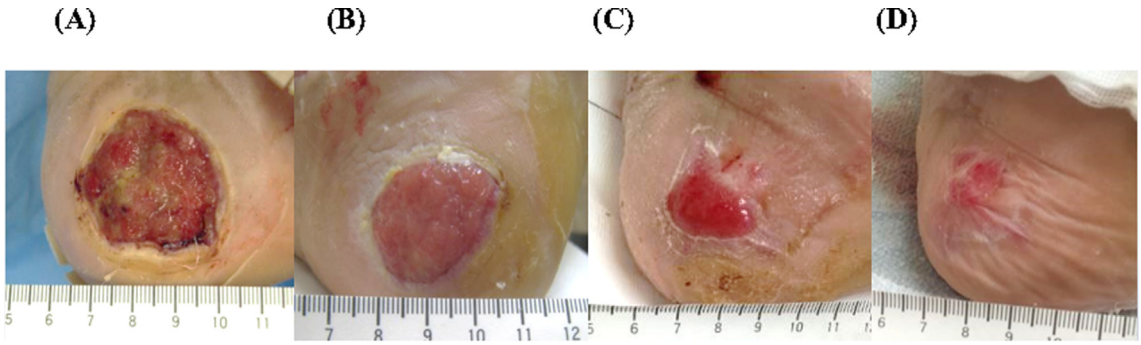

Fig. 3 – A 56-year-old male in the collagen group. The diabetic foot ulcer was located at the medial aspect of heel. The initial size was 8.3 cm^2 measured by planimetry. Status at (A) baseline, (B) 2 weeks after collagen dressing application, (C) 4 weeks after treatment with >50% healing, and (D) 8 weeks after treatment with complete healing.

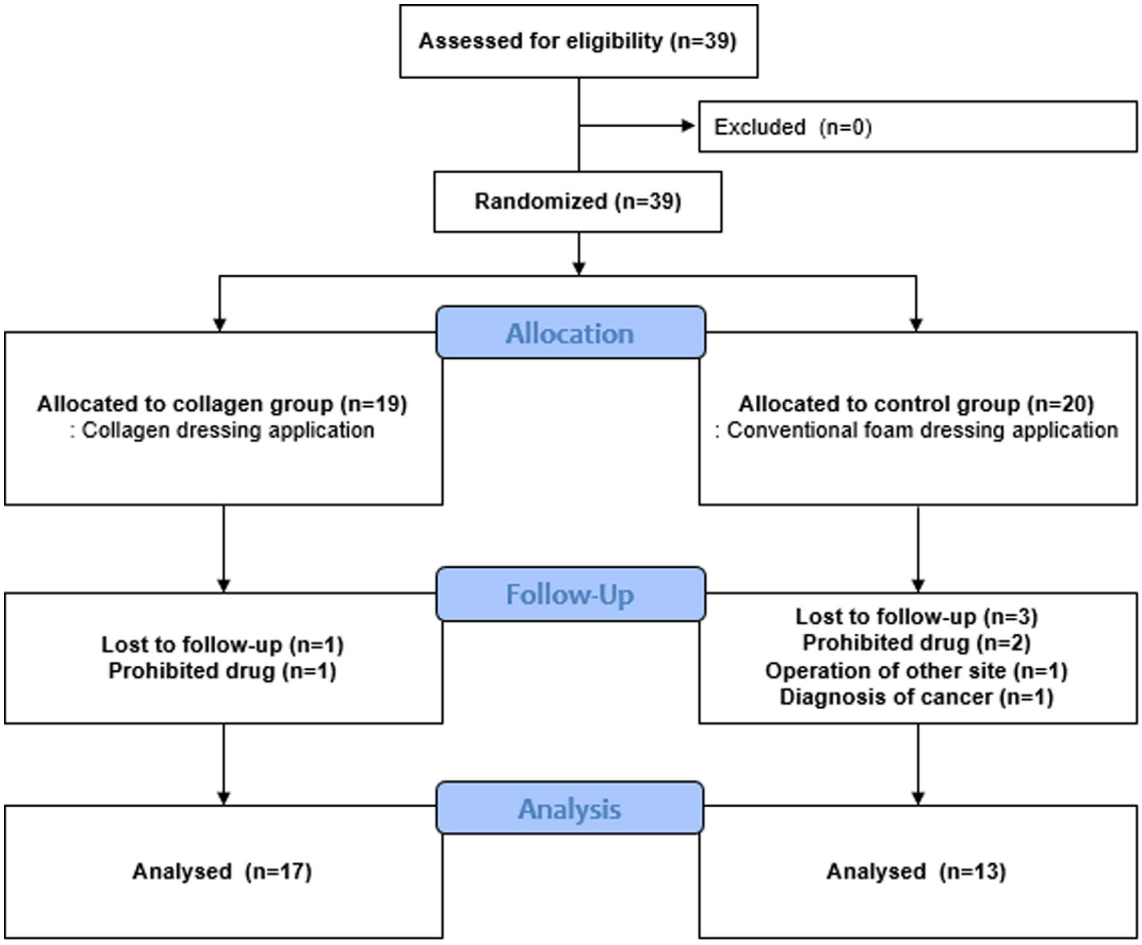

Fig. 4 – The CONSORT diagram patient flow in the study. Abbreviations: CONSORT, CONsolidated Standards Of Reporting Trials.

groups. In particular, mean hemoglobin A1c (HbA_{1C}) levels at baseline were similar for the two groups: 7.1 ± 1.2% (62.3 ± 23.4 mmol/mol) in the collagen group versus 7.8 ± 2.1% (54.6 ± 12.9 mmol/mol) in the control group ($P = .299$). Other medical variables including blood pressure, heart rate, nutritional status indicated by serum albumin, number of serum white blood cells, smoking status, and types of offloading devices were also not significantly different between the two groups. There were no statistical differences between groups with respect to baseline DFU characteristics such as duration, anatomic location, or ulcer grade.

3.2. *Primary and secondary endpoints*

The initial ulcer sizes (mean ± standard deviation) were 4.98 ± 6.59 cm^2 in the collagen group and 4.49 ± 6.56 cm^2 in the

Table 1 – Demographics and initial medial status by group.

	Collagen (n = 17)	Control (n = 13)	P value
Demographic factors			
Age (years)	62.8 ± 13.0	53.0 ± 14.7	0.069
Female gender, n (%)	5 (29.4)	2 (15.4)	0.427
BMI (kg/m^2)	24.6 ± 3.2	23.6 ± 2.2	0.325
Duration of diabetes (years)	19.5 ± 7.2	20.1 ± 8.6	0.926
Medical status at screening			
Systolic BP (mmHg)	130.0 ± 19.3	124.8 ± 15.0	0.411
Diastolic BP (mmHg)	72.8 ± 13.2	73.8 ± 10.4	0.818
Heart rate (/min)	81.6 ± 8.0	90.5 ± 14.3	0.052
White blood cells (x 10^3/μL)	7.4 ± 2.2	7.9 ± 1.4	0.480
Hb (g/dL)	12.2 ± 2.1	11.4 ± 1.6	0.325
HbA_{1C}, % (mmol/mol)	7.1 ± 1.2 (62.3 ± 23.4)	7.8 ± 2.1 (54.6 ± 12.9)	0.299
Albumin (g/dL)	3.8 ± 0.3	3.7 ± 0.2	0.254
Smoking, n (%)			0.789
Non-smoker	10 (58.8)	6 (46.2)	
Former smoker	6 (35.3)	6 (46.2)	
Current smoker	1 (5.9)	1 (7.6)	
Offloading devices			
Offloading shoe with rigid-rocker sole	13 (76.5)	10 (76.9)	0.951
Splint	3 (17.6)	2 (15.4)	
Wheelchair	1 (5.9)	1 (7.7)	

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DFU, Diabetic foot ulcer; Hb, hemoglobin; HbA_{1C}, hemoglobin A1c; n, number of subjects with characteristic; SD, standard deviation. Chi-Square test, Mann-Whitney test, Mean ± standard deviation.

Table 2 – Baseline characteristics, size, and change of DFUs by group.

	Collagen (n = 17)	Control (n = 13)	P value
Baseline DFU characteristics			
DFU duration prior to enrolment (weeks)	17.4 ± 9.0	12.7 ± 6.7	0.141
Side of DFU, n right foot (%)	9 (52.9)	8 (61.5)	0.721
Location of DFU, n (%)			0.995
Toe	3 (17.6)	2 (15.4)	
Interphalangeal area	1 (5.9)	1 (7.7)	
Sole	6 (35.3)	5 (38.4)	
Heel	4 (23.5)	3 (23.1)	
Malleolus	2 (5.9)	1 (7.7)	
Other	1 (5.9)	1 (7.7)	
Wagner grade, n (%)			0.374
Grade I	16 (94.1)	13 (1 0 0)	
Grade II	1 (5.9)	0	
DFU size and change (cm^2)			
Initial size	4.98 ± 6.59	4.49 ± 6.56	0.829
Last follow-up	0.59 ± 1.95	1.70 ± 3.57	**0.034**
Δ of DFU size	4.39 ± 4.95	2.24 ± 2.81	**0.027**

Abbreviation: DFU, diabetic foot ulcer. Chi-Square test, Mann-Whitney test. Mean ± S.E.M. (standard error of mean). Boldface indicates statistical significance ($P < .05$).

control group ($P = .829$, Table 2). At the end of the trial, mean ulcer size was significantly decreased in the collagen group compared with the control group (0.59 ± 1.95 cm^2 versus 1.70 ± 3.57 cm^2, respectively; $P = .034$, Table 2). The mean size reduction was also greater in the collagen group compared to the control group (4.39 ± 4.95 cm^2 versus 2.24 ± 2.81 cm^2, respectively; $P = .027$, Table 2). The primary study endpoint was complete healing rate during the 12-week study period. The collagen group had a significantly higher proportion of patients who achieved complete healing compared with the control group (82.4% (14/17) versus 38.5% (5/13), respectively; $P = .023$, Table 3).

Healing velocity, time to achieve a 50% reduction in ulcer size, and time to complete ulcer healing were measured as secondary endpoints. Healing velocity was significantly greater, by 8.44% per week, in the collagen group compared with the control group (17.85 ± 14.61% per week versus 9.41 ± 8.28% per week, respectively; $P = .011$, Table 3, Fig. 5). Consistent with the healing velocity results, Kaplan-Meier survival analysis showed that the median time to decrease DFU

Table 3 – Clinical outcomes by group.

	Collagen (n = 17)	Control (n = 13)	P value
Primary endpoint			
Complete healing rates	82.4% (14/17)	38.5% (5/13)	**0.023**
Secondary endpoints			
Healing velocity (cm^2/week)			
Mean ± SD	0.55 ± 0.44	0.29 ± 0.42	**0.001**
Median (range)	0.44 (1.58–0.12)	0.11 (1.47–0.03)	
Healing velocity (%/week)			
Mean ± SD	17.85 ± 14.61	9.41 ± 8.28	**0.011**
Median (range)	11.81 (50.00–5.83)	6.55 (33.33–2.01)	
50% size reduction [a]			
Median time (days)	21.00	42.00	
Hazard ratio (95% CI)	1.94 (1.17–5.04)		**0.037**
Complete healing [a]			
Median time (days)	63.0	n.a.	
Hazard ratio (95% CI)	2.90 (1.20–7.26)		**0.025**

Values are expressed as mean ± standard deviation for continuous variables. Categorical variables are expressed as the number and percent of patients with the measured characteristic. Abbreviations: CI, confidence interval; SD, standard deviation. Boldface indicates statistical significance ($P < .05$).

[a] Kaplan-Meier survival analysis.

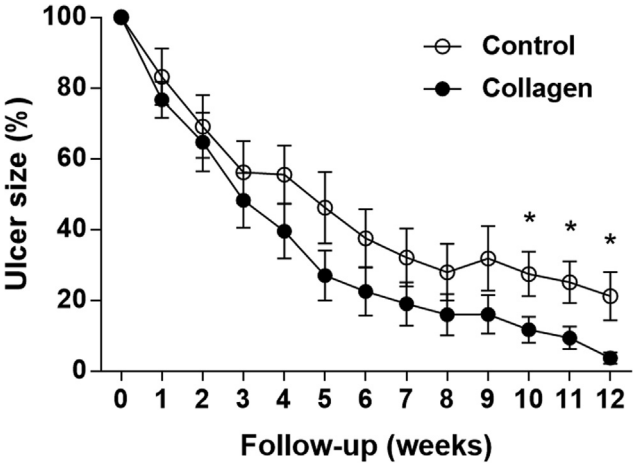

Fig. 5 – Plot of ulcer size during the study period.

size by 50% was significantly shorter in the collagen group than in the control group (21 versus 42 days, respectively; hazard ratio = 1.94, P = .037, Fig. 6A). The median time to complete ulcer healing was also significantly shorter in the collagen group compared with the control group (63 days versus not reached, respectively; hazard ratio = 2.90, P = .025, Fig. 6B).

3.3. *Safety*

Routine laboratory tests (complete blood count, serum chemistry screen, and urinary analysis) were performed at the screening visit and weeks 4 and 12. There were no significant laboratory result changes in either group during the trial. A total of 7 adverse events in 30 patients were noted. In the collagen group, adverse events were reported in four cases including pain, discomfort, and skin sensitization. In comparison, three adverse events including pain or discomfort, skin sensitization, and odor occurred in the control group (Table 4). Based on analyses of the laboratory results and physical examinations, there were no infective events during the study period. No safety issues were identified related to the collagen dressing material.

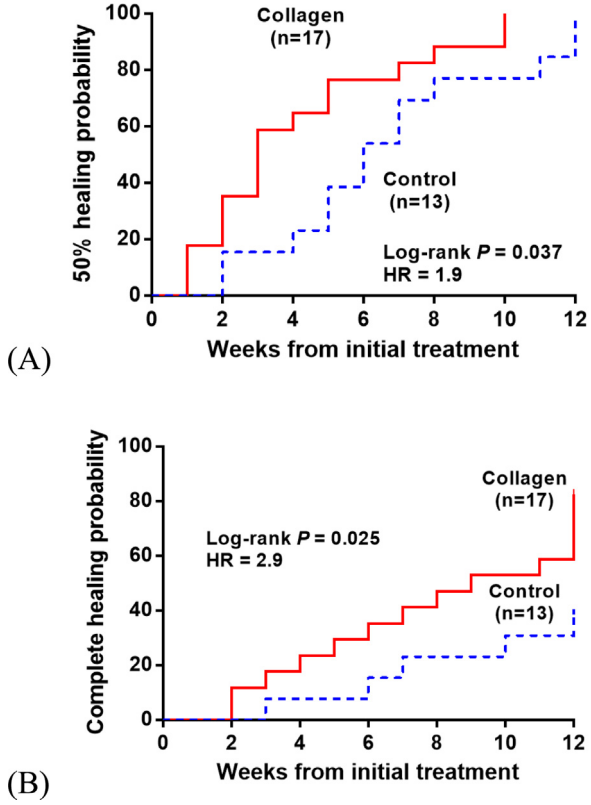

Fig. 6 – Kaplan-Meier plots with log-rank testing for complete healing. Abbreviation: HR, hazard ratio.

Table 4 – Adverse events by group.

	Control (n = 13)	Collagen (n = 17)	Odds ratio (95% CI)[†]	P value[*]
Infective events (n)	0	0	4.9 (2.1–11.7)	<0.001
Pain or discomfort (n)	1	2	1.3 (0.6–2.6)	0.471
Maceration (n/changes)	0.6	0.9	1.7 (0.8–3.8)	0.269
Skin sensitization (n)	1	2	2.1 (0.9–5.0)	0.128
Odor (n)	1 (5.8%)	0 (9.5%)	1.7 (0.5–5.8)	0.481

[*] Fisher's exact test.
[†] CI, confidence interval.

4. Discussion

Due to impaired wound healing, patients with DFUs require longer treatment periods, which are associated with lower quality of life and higher risk of limb amputation. This has led to the development of various dressing materials to increase wound healing rates.

The moist wound environment plays an important role in recruiting both host defenses and the cell populations that help promote healing. On this basis, most dressing materials are designed to maintain a moist environment and absorb exudates. To achieve these goals, foam dressings contain hydrophilic polyurethane foams, hydrogel dressings consist of cross-linked insoluble polymers, and hydrocolloid dressings are occlusive dressings. Dressing materials with antimicrobial effects, such as iodine or silver-impregnated dressings, are also widely used. Positively charged silver ions can disrupt bacterial cell membranes and are useful to treat DFU accompanied by bacterial infection [23,24]. They are also used in combination with collagen. Alginate dressings are highly absorbent and can be combined with collagen to treat DFU. Donaghue et al. [25] reported that the healing rate in the group of 90% collagen and 10% alginate was superior to that in the control group. Dermal substitutes and commercial skins are being used to treat burns and in reconstructive surgeries [26], but few studies have reported their use in patients with DFUs. In this study, we used 100% collagen as a dressing material. When we compared a purity of collagen with other collagen products, the purity of collagen in this study was high. Also, electron microscope images showed that the collagen dressing material had a porous structure and high biocompatibility. The high purity and high biocompatibility of the collagen might support excellent clinical results of this study.

Collagen may be harvested from a variety of sources including living and nonliving bovine, porcine, and equine skin. Collagen promotes cellular recruitment and wound healing. In the clinical setting, collagen is used in various forms such as powders, gels, and sponges. A collagen sponge may act as a template for tissue growth. Collagen materials are useful dressing materials because they show low toxicity without severe complications. Mulder et al. described results from a study of a human platelet-derived growth factor-B formulated in a bovine collagen gel for neuropathic DFUs [27]. Among the 12 patients, complete healing was noted at 3 months after the treatment in 10 patients. There were no toxic or adverse effects in their study.

Xenograft collagen dressings have been used and evaluated. Clerici et al. studied a dermal substitute with bovine type I collagen to preserve maximal foot length in diabetic foot wounds [28]. Overall, 26 of 30 patients showed healing of the distal amputation stump with an average healing time of 10 weeks. No additional proximal amputation was required in any patients. Offloading was not described. Liao et al. used porcine young collagen wettable membrane and growth factor in six patients [29]. Of the five patients who completed the study, improved healing was observed in three (60%). However, offloading was not described, and the sample size was small. Marston et al. reported the study of porcine-derived collagen injectable matrix scaffolding composed of gelatin [30]. Six patients with DFUs persisting longer than 2 months were enrolled, and immediate responses were noted in all cases. The average decrease in wound size was 72% at 2 weeks after treatment ended.

Although various studies have reported the effects of collagen dressing materials, some were based on small sample sizes, while others did not clearly describe offloading. Some were retrospective, and some did not give a firm definition of wound healing. Some investigations found no significant difference between collagen and other dressing materials. Landsman et al. [31] examined 26 patients with DFUs. They used an extracellular collagen matrix derived from the submucosa of porcine small intestine and found no differences in the time or rate to closure between the collagen dressing and saline-moistened gauze dressing groups.

In the present study, type I collagen dressing did not cause severe adverse events or toxicity. On this basis, type I collagen dressings can be safely used for human patients. Over the 12-week study period, there was a significant ulcer size reduction and greater healing velocity in the collagen group compared to the control group. The mean healing velocity was 0.55 ± 0.44 cm^2/week in the collagen group and 0.29 ± 0.42 cm^2/week in the control group ($P = .001$). The complete healing rates were 82.4% (14/17) and 38.5% (5/13) in the collage and control groups respectively ($P = .023$). Our results indicate that 100% collagen is a safe and effective wound dressing for DFUs.

Limitations of this study include a relatively small sample size and variable wound sizes and locations. Although DFU patients commonly have comorbidities such as infection or peripheral arterial occlusive diseases, we excluded such individuals, which might be another shortcoming.

In conclusion, this study supports the efficacy and safety of collagen dressing for chronic DFUs. Future studies with larger populations and longer-term follow-up are needed.

Acknowledgments

This study was supported in part (collagen dressing materials) by providing from SK bioland Co., Ltd. (Cheongju, South Korea).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contribution statement

Author Contributions. K.H.P researched clinical data and conducted data analyses, and wrote the manuscript. J.B.K., J.H.P. and J.C.S. collected clinical data and edited the manuscript. S.H.H and J.W.L. reviewed the manuscript and are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. reviewed the manuscript.

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