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Wound treatment with hyaluronic acid and silver sulfadiazine promote better epithelialization compared to polyurethane and normal saline in diabetic foot ulcer

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ABSTRACT

Background: Diabetic foot ulcer, one of the chronic complication of diabetes mellitus that has a high morbidity and mortality rate. The primary conventional treatment for diabetic ulcer was debridement, followed by wound treatment as local control to promote healing and epithelization. There are many different methods on wound treatment; however only few types of research compared the efficacy. This study aims to compare the combination of hyaluronic acid and silver sulfadiazine with polyurethane or normal saline in diabetic foot ulcer treatment.

Method: A randomized clinical study was conducted to compare the efficacy of silver sulfadiazine with hyaluronic acid, polyurethane and normal saline in Wagner 3 and 4 diabetic foot ulcer as the main treatment until 3 weeks post debridement. Several variables assessed in this study, such as epithelialization area, granulation percentage, and ankle diameters. Appropriate statistical analysis was conducted with SPSS version 17 with $p < 0.05$ considered significant.

Result: The median tissue epithelialization area after 3 weeks of wound treatment on normal saline group was 1.62 cm^2 (IQR: 0.2 -2.22), on polyurethane group was 2.79 (IQR: 2.39 -3.19 cm^2), and silver sulfadiazine with hyaluronic acid group was 3.1 (IQR: 2.1-4.1) cm^2 ($p<0.05$). There was no significant difference in the percentage of granulation ($p=0.136$) and ankle circumference ($p=0.74$) among treatment groups.

Conclusion: Silver sulfadiazine with hyaluronic acid promote the wound healing process in Wagner 3 and 4 diabetic foot ulcer after 3 weeks by promoting a better tissue epithelization compared to normal saline and polyurethane.

Keywords: Diabetic foot ulcer, Hyaluronic acid, epithelialization

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Introduction

Diabetic Foot Ulcer (DFU) is a chronic complication of Diabetes Mellitus (DM) that occurs among roughly 15% of patients and contribute an unnecessary health burden worldwide.[1] Singh et al. (2005) explain the effects of DFU on DM patients, namely disruption of physical, emotional, productivity, and financial conditions.[2] DFU is an ulcer or injury due to damage or death of the inner tissue associated with various degrees of peripheral vascular disease in inferior extremity and can be accompanied by infection, which is a direct or indirectly related to metabolic derangement experienced in DM. Skin necrosis and the occurrence of gangrene are forms of ulcers. Gangrene is a necrosis that occurs in the skin and the underlying structures, namely muscles, tendons, joints, and bones.[3] Various variants have been used to classify DFU. The International Working Group of the Diabetic Foot (IWGDF) recommends a classification system based on 5 categories, namely: perfusion, extension/size, depth / soft tissue loss, infection, and sensation.[4]

As the development of science, technology, and medicine, many innovations in the treatment methods of DFU were presented, with the advantages and disadvantages of each. The wound dressing is part of DFU management. Dressing mistakes can interfere with DFU healing. Ideally, dressing should relieve symptoms, provide wound protection, and encourage healing. At present, no method can fulfill all of these for the treatment of DFU patients. Even more, research to compare the effectiveness of dressings is rarely carried out.[4]

Each dressing category has specific characteristics that aid selection. The non-adhesive dressing is simple, inexpensive, and well-tolerated. Dressing with foam and alginate is highly absorbent and effective for productive wounds. Hydrogels facilitate autolysis and provide benefits in the management of ulcers containing necrotic tissue. Dressings that contain iodine and silver can help in managing infection. The occlusive dressing should be avoided for infected wounds, and exudation of

ulcers requires more frequent dressing replacement to reduce surrounding skin maceration. The applied dressing often changes according to wound on periodic evaluation. The dressing that is used must be adjusted to the characteristics of the ulcer, patient requirements, and cost.[4]

Hyaluronic acid (HA) is known to play a pivotal role in every phase of wound healing, starting from the inflammatory phase, HA facilitates the initial adhesion of cytokines-activated lymphocytes in the endothelium. In the granulation phase, HA promotes cell mitosis and increases cell migration and angiogenesis. In the reepithelization period of HA associated with proliferation of keratin cells and facilitating their migration through CD44-mediated mechanism and in the remodeling phase, HA reduces collagen deposits and induces scar tissue absorption.[5,6]

In addition, different dressing methods also have a particular benefit. Polyurethane has high absorption, the cushion covers and protects the body surface, is able to condition the wound environment to remains moist, fills the cavity of the ulcer, reduces wound dead space, adjusts to the shape of the wound and absorbs excess exudate to minimize the risk of maceration.[7-9]

In our hospital, much of the care were conducted with conventional protocol due to various reason, including cost. Although traditional care of wound was cheapest, if it there are alternatives such as wound dressing with polyurethane and Silver sulfadiazine preparations with Hyaluronic acid that shorten the duration for wound healing, then it will translate to lower cost of overall burden mainly for the patients. However, no study has been conducted to compare the effectiveness of conventional wound dressing methods (NaCl 0.9%), combination of Silver sulfadiazine preparations (SSD) with Hyaluronic acid, and modern dressings (Polyurethane). In this regard, the researcher aims to find out which dressing method has advantages according to the ideal dressing for wound healing in patients with diabetic foot ulcers.

METHODS

A randomized clinical trial was conducted among 59 patients with DMDF Wagner 3 or 4 at Surgery Department, Faculty of Medicine Universitas Udayana/Sanglah General Hospital Bali-Indonesia from March 2017 until March 2018. Patients age ranged between 40-70 years with blood glucose levels < 200 g/dL were included in this study. Patients with chronic liver failure, renal failure, on chemotherapy and corticosteroid, albumin < 2.5 g/dL and Hb < 10 g/dL were excluded in this study. Patients whose clinical characteristics fulfill the inclusion and exclusion criteria were recruited consecutively and randomly divided into 3 groups. The first group was treated with 0.9% NaCl (conventional DFU wound care), the second group treated with polyurethane and the third group was treated with Silver Sulfadiazine and Hyaluronic acid preparation (SSD+HA).

Wound care was carried out daily and applied to all groups. The effect of treatment (outcome) was evaluated by measuring ankle diameter, granulation percentage and the area of tissue epithelialization. A baseline measurement was carried out after debridement and compared with measurement after three weeks of each wound treatment. Appropriate statistical analysis was applied to determine the presence of statistically significant difference in mean of the treatment outcome among groups and $p<0.05$ was considered significant. All of data were analyzed using SPSS version 17 for Windows.

RESULT

A total of 59 patients included in this study. The subject characteristic showed in Table 1. The highest mean age was found in the SSD+HA group (57.21 ± 11.86 years). Female was predominant in the SSD+HA group (64.3%), whereas male was predominant in the Polyurethane group (61.9%). The most level education among respondents was Senior High School in all groups (58.3% vs. 42.9 vs. 50.0). The DM-2 Wagner 3 was predominant in NaCl 0.9% (62.5%) and Polyurethane (66.67%) (Table 1).

Other parameters obtained from laboratory test were also presented, summarized in Table 2. The leucocyte and neutrophil counts were higher in the NaCl 0.9% group (16.74 (6.35 – 27.13) µ/µL; 13.91 (8.16 – 19.66) µ/µL). However, the hemoglobin, HbA1c, and albumin levels were the lowest in SSD+HA group (10.63 (8.80 – 13.18) g/dL; 7.6 (4.33 – 10.87) %; 2.85 (2.03 – 3.67) g/dL) (Table 2)

Comparison of ankle difference, granulation, and extent of epithelialization in all three treatment groups in the Kruskal – Wallis test seen in Table 3. As Multivariate analysis as shown in Table 3, the were no statistical differences in ankle circumference (p = 0.74) and granulation percentage (p=0.136) among the treatment group — the area of epithelialization shown a statistically significant difference among treatment groups (p<0.0001). Groups of patients treated with SSD+HA on average have the most considerable area of epithelization, followed by polyurethane groups and lastly the saline groups.

As Multivariate analysis, as shown in Table 3, the were no statistical differences in ankle circumference (p = 0.74) and granulation percentage (p=0.136) among the treatment group — the area

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Table 1. Clinical Characteristics of Subjects among Treatment Groups

Variable	Treatment Groups		
	NaCl 0.9% (n=24)	Polyurethane (n=21)	SSD+HA (n=14)
Age (year) (Mean ± SD)	53.3 ± 11.92	57.95 ±10.78	57.21 ± 11.86
Sex (n, %)			
Male	12 (50)	13 (61.9)	5 (35.7)
Female	12 (50)	8 (38.1)	9 (64.3)
Education (n, %)			
Elementary School	6 (25)	8 (38.1)	3 (21.4)
Junior High School	3 (12.5)	1 (4.8)	2 (14.3)
Senior High School	14 (58.3)	9 (42.9)	7 (50.0)
University Degree	1 (4.2)	3 (14.2)	2 (14.3)
Duration of DM (yr)			
Median (Interquartile range)	5.0 (2.25 – 7.75)	7.0 (4.0 – 10.0)	7.0 (4.0 – 10.0)
Ulcer degree (n, %)			
Wagner 3	15 (62.5)	14 (66.67)	5 (35.7)
Wagner 4	9 (37.5)	7 (33.33)	9 (64.3)

Table 2. Clinical Laboratory Parameters of Subjects among Treatment Groups

Variable	Treatment Groups (Median (IQR))		
	NaCl 0.9% (n=24)	Polyurethane (n=21)	SSD+HA (n=14)
Leucocyte (µ/µL)	16.74 (6.35 – 27.13)	13.18 (2.59 – 23.77)	12.87 (5.87 – 19.87)
Neutrophil (µ/µL)	13.91 (8.16 – 19.66)	11.23 (2.53 – 19.93)	10.69 (4.94 – 15.63)
Monocyte (µ/µL)	0.84 (0,35 – 1.33)	0.80 (0.10 – 1.50)	0.88 (0.02 – 1.72)
Haemoglobin (g/dL)	11.35 (8.80 – 13.9)	11.48 (8.72 – 14.24)	10.63 (8.80 – 13.18)
Random Blood Glucose (mg/dL)	193.50 (168.7 – 218.2)	181.0 (119.5 – 242.5)	184.0 (156.5 – 211.5)
HbA1c (%)	9.20 (3.05 – 15.35)	9.1 (5.55 – 12.65)	7.6 (4.33 – 10.87)
Albumin (g/dL)	2.95 (2.25 – 3.65)	3.0 (2.13 – 3.87)	2.85 (2.03 – 3.67)

Table 3. Comparison of ankle circumference, Granulation, and Epithelialization among Treatment Groups

Outcome	Groups	Subjects (n=59)	Mean Rank	Statistic
Ankle Difference	NaCl 0.9%	24	30.65	x^2 =5.218
	Polyurethane	21	34.79	df = 2
	SSD+HA	14	21.71	p = 0.74
Granulation (%)	NaCl 0.9%	24	25.88	x^2 = 3.995
	Polyurethane	21	30.19	df = 2
	SSD+HA	14	36.79	p = 0.136
Width of Epithelialization	NaCl 0.9%	24	19.42	x^2 = 19.254
	Polyurethane	21	32.60	df = 2
	SSD+HA	14	44.25	p <0.0001

of epithelialization shown a statistically significant difference among treatment groups (p<0.0001). Groups of patients treated with SSD+HA on average has the largest area of epithelization, followed by polyurethane groups and lastly the saline groups (Table 3).

Figure 1 illustrates the differences in area of epithelialization among the three treatment groups, wherein the Saline treated group, area of epithelialization was found with a median of 1.62 cm2 and IQR 0.2 - 2.22 cm2, in the polyurethane treatment group the median value was 2.79 cm2 and IQR 2.39 - 3.19 cm2, while in the SSD + HA treatment group, the median was 3.1 cm2 and IQR was 2.1 - 4.1 cm2 with p = <0.001, which was statistically significant.

From Table 4. it was found that the variables of age, gender, educational background, duration of DM, and ulcer degree did not give a difference in results that were statistically significant (p□ 0.05).

Discussion

Wound care is part of DFU management. Ideally, the treatment given should relieve symptoms, provide protection, and facilitate wound healing. The use of saline as a regimen in wound care has been known for a long time, as is the case with polyurethane which has high absorption, protects wound surfaces, fills the space of the ulcer, reduces dead space, optimizes wound healing.[3,7-9]

Methods of wound care using the Silver Sulfadiazine and Hyaluronic acid regimen was said to be better in managing infectious wounds. Hyaluronic acid plays a role in every phase of wound healing, starting from facilitating primary adhesion of endothelial cytokines activated lymphocytes, promoting cell mitosis, increasing cell migration and angiogenesis, and related to keratin cell proliferation and its migration through CD 44-mediated mechanism. Due to these critical roles, Hyaluronic acid was expected to help reduce collagen deposits and induces absorption of scar tissue.[3,6]

From this information, the authors conducted a study to compare the effectiveness of the three wound treatment methods and found significant epithelialization differences in the Silver sulfadiazine and Hyaluronic acid treatment group when compared with polyurethane and 0.9% NaCl treatment groups. The normal saline treatment group epithelialization was found with a median of 1.62 cm^2 (IQR 0.2 - 2.22 cm^2), in the polyurethane treatment group the median value was 2.79 cm^2 and (IQR 2.39 - 3.19 cm^2), whereas in the treatment group with Silver sulfadiazine and Hyaluronic acid was found the median is 3.1 cm^2 (IQR is 2.1 - 4.1

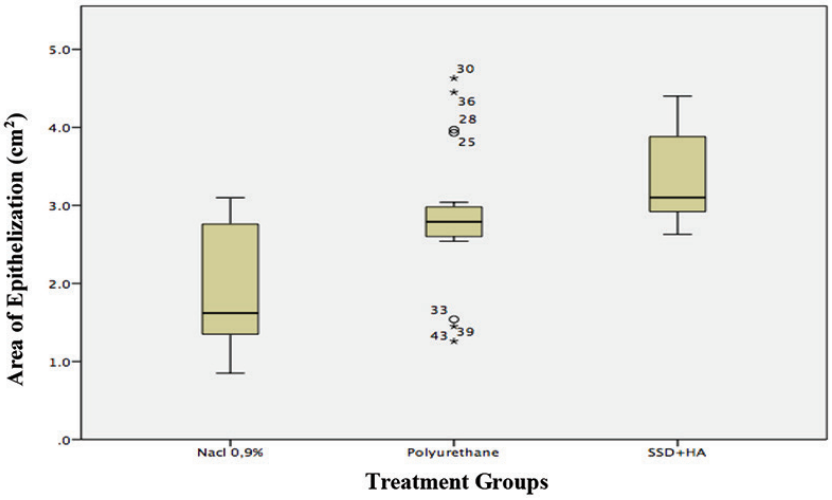

Figure 1. Distribution of area of epithelization among treatment groups

Table 4. ANCOVA analysis comparison of the area of epithelialization by controlling for variables of age, sex, educational background, duration of DM, and ulcer degree

Characteristic	F	P	R^2
Sex	1.301	0.259	0.025
Age	0.115	0.735	0.002
Duration of DM (years)	0.006	0.938	0.000
Degree of ulcer (Wagner)	0.158	0.693	0.003
Education	0.257	0.614	0.005
Groups	12.526	<0.001	0.329

cm^2) with a value of p <0,001.

The results obtained are comparable with several studies that have been done previously, including a meta-analysis conducted by Chen et al., about the cure rate of diabetic foot treated with Hyaluronic acid in 328 patients. The odds ratio (OR) of recovery rate among diabetic foot treated with HA were ranged from 1.19 - 8.86, with the overall OR being 1.71 (p = 0.047; 95% confidence interval = 1.01 to 2.90).[10] Dereure et al., with a double-blind randomized controlled trial, measured how many ulcer size reduction after being treated for 45 days with Hyaluronic acid compared with controls. Among 101 patients, the authors found a significant difference in reduction of ulcer size (p = 0.002) in treatment with Hyaluronic acid (39±6%) compared in the control group (5± 9%).[11] The same results obtained by Abbruzesse et al., with a Prospective Double-Blind Randomized Trial study involving 30 patients divided randomly into treatment and control groups. The treatment groups given a novel gel formulation, containing amino acids and hyaluronic acid obtained a reduction of ulcer size by 58.7% in the treatment group and 23.4% in the control group (p= 0.05).[12]

From the perspective of healing rate, several studies also report a better healing rate for diabetic wound treated with hyaluronic acid. Lee et al. with a prospective randomized placebo control in 34 patients treated with Hyaluronic acid and placebo, and followed for 12 weeks, found complete healing rates of 84.6% in the treatment group and 41.6% in the control group (p = 0.041).[13] Likewise, result obtained by Tankova et al., treatment with hyaluronic acid got ulcer healing rate of 93% while in the control group was 82% (p = 0.008).[14] Therefore, many studies support the superiority of hyaluronic acid-contained preparation in diabetic foot ulcer wound care.

Conclusion

Silver sulfadiazine with hyaluronic acid was superior to promote the wound healing process in Wagner 3 and 4 diabetic foot ulcer after 3 weeks by promoting tissue epithelization better compared to normal saline and polyurethane.

ETHICAL CLEARANCE

This study has been obtained the ethics approval from the Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia prior to the study being conducted

Conflict of Interest

The authors declare that there is no competing interest regarding the manuscript.

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Author Contribution

Made Kurniawan AS is responsible for data gathering, data analysis, and write the results of the study. I Nyoman Semadi and I Gede Raka Widiana are responsible for study concept and supervised the study.

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