Original Research Article

Evaluation of Honey and Povidone Iodine Dressings on the Healing of Wagner 2 Diabetic Foot Ulcers: A Randomized Trial

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ABSTRACT

Diabetic foot ulcers (DFU) are challenging complications which result from pathophysiologic tissue changes in diabetes mellitus. These ulcers require appropriate dressings to boost their healing. Reports on the therapeutic efficacy of honey and povidone iodine stimulated the quest to enhance knowledge on effective and available dressing materials for DFU treatment.

Aim: To compare the efficacy of honey and povidone iodine dressings on the healing of Wagner Grade 2 DFU.

Study design: This was a randomized controlled trial comparing the rate of Wagner grade 2 DFU healing following of honey and povidone iodine dressings at the University of Port Harcourt Teaching Hospital, Port Harcourt over a year duration.

Methodology: Thirty subjects with Wagner grade 2 DFU were recruited (17 males; aged 47-65 years). Data on socio-demographics, HbA1c, ulcer contraction, exudate characteristics and oedema resolution were obtained and analysed using Statistical Package for the Social Sciences (SPSS) 20.0. A p-value <0.05 was considered significant.

Results: The mean change in ulcer diameter was 0.69±0.17mm and 0.61±0.11 mm for the honey and povidone iodine groups respectively (p-value=0.062) in the first week, and 1.17±0.19mm and 1.08±0.16mm for the honey and povidone iodine groups respectively (p-value=0.124) in week 4. By week 5, all ulcers in the honey group were healed, while one ulcer lasted beyond week 6 in the povidone group. The mean change in mid-foot circumference (MFC) was 0.62±0.52cm and 0.29±0.35cm for the honey and povidone iodine groups respectively (p-value 0.051), in week 2.

Conclusion: Honey and povidone iodine dressings have comparable healing effects in the treatment of Wagner 2 DFU, with the honey dressings being marginally more efficacious.

Keywords: Diabetic foot ulcer, wound dressing, healing, povidone iodine, honey

1. INTRODUCTION

The natural history of diabetes mellitus is laden with diverse complications if glycemic control remains inadequate.[1] Diabetic foot ulcers (DFU), a major class of complications arise from the combined effects of angiopathy, neuropathy, arthropathy, trauma and reduced immunity which occur in diabetes mellitus.[2][3][4] Hyperglycemia and DFU are linked by intricate molecular dysfunctions that lead to accelerated atherosclerosis, delayed development of collateral vasculature,

and thrombosis that impair the healing process of wounds.[2][3] Polymicrobial invasion and proliferation are enhanced by autonomic dysfunction, anhydrosis with dry cracked skin and leukocyte dysfunction function respectively. [2][3][5]
The prevalence of DM foot lesions ranges from 0.9% to 8.3% in Nigeria [3][6][7] and 6.3% globally.[3] Over 15% of diabetics develop DFU during their lifetime, often associated with avoidable physical, psychological and economic disability.[2][3][8] DFU result in over 80% of non-traumatic lower limb amputations which are preventable with timely and adequate treatment.[3][7] The estimated mortality rates for DFU development are 5% in the first 12 months and 42% in the first five years.[9] The growing population, increasing life expectancy and projected rise in the incidence of diabetes all point to the worsening burden of diabetic complications. [3][10] Multidisciplinary management with emphasis on patient education, regular foot examinations, good glycaemic control, and aggressive intervention (debridement, antibiotic therapy, regular inspection and dressing) remain the bedrock of DFU treatment. [3][11][12]
Wound dressings are integral to DFU management, and should relieve symptoms, protect the wound, and provide a moist environment that encourages healing, absorb exudates, conditions comparable to the body's internal milieu; and additionally, control odour and be cost-effective. [2][8][13][14] There is yet no ideal dressing for DFU. [12][13] The choice of dressing depends on the wound characteristics i.e. appearance, and exudate. [13]

The therapeutic use of honey began centuries ago.[5][8] Honey and povidone iodine have generated renewed interest for use in DFU treatment, especially in developing countries. [5][14]

Honey is a supersaturated sugar solution produced by honey bees, from the nectar or other plant secretions. [15][16][17] It consists of 80–85% carbohydrate (mostly glucose and fructose), 15–17% water, 0.1–0.4% protein, 0.2% ash and little amounts of amino acids, enzymes, vitamins and phenolic antioxidants. [16][17][18] It also contains hydrogen peroxide, inhibin, and has high acidity(pH 3.2 - 4.2) which inhibit bacterial proliferation. [5][14][19] When used topically, honey reduces oedema and inflammation, debrides necrotic tissues, enhances angiogenesis and granulation tissue, prevents biofilms formation, deodorizes infected wounds, reduces pain, promotes epithelisation and minimizes scarring. [5][8][14][20]

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Povidone-iodine consists of a loose mixture of iodine and a non-ionic surfactant. [21][22][23] It has significant affinity for cell membranes and enhances healing by modulating the activity of specific cells of the immune system.[22] Its antimicrobial activity is maximal at 0.1%–1% (after dilution) due to the weakened link between the carrier polymer and the iodine molecules, leading to the increased concentration of elemental "free" iodine in solution.[22][23] Hence, it is lethal to gram-negative and gram-positive bacteria, viruses, protozoa and fungi, amoebic cysts, and protozoa. [22][24][25] Despite its widespread use, acquired resistance to it remains rare as it acts across several bacterial sites.[23][25] Additionally, it possesses anti-inflammatory properties, and an established safety profile. [23][24][25]

Several DFU classification systems exist.[4][26] However, the Wagner classification which considers the ulcer depth, presence of osteomyelitis, and amount of tissue gangrene, is most widely utilized. [26][27]

Table 1: Wagner Grading of Diabetic Foot Ulcers (1981) [26][27]

Grade	Description
0	Skin intact but bony deformities produce a "foot at risk"
1	Localized, superficial ulcer
2	Deep ulcer to tendon, bone, ligament, or joint
3	Deep abscess, osteomyelitis
4	Gangrene of toes or forefoot
5	Gangrene of entire foot

Reduction in ulcer diameter, evolution of exudate characteristic to serous exudate and oedema resolution are pointers to satisfactory wound healing, and can be objectively assessed as outcome measures of wound healing. [5][28][29][30] Thus the knowledge of effective, cheap and readily available dressing materials will enhance DFU management.

2. METHODOLOGY

2.1 Study Design

This was a randomized controlled trial (RCT) comparing the rates of wound healing vis à vis ulcer contraction following honey and povidone iodine dressing among patients with Wagner 2 DFU who presented to the UPTH via the orthopedic clinic and medical wards between April 1st 2017 and April 30th, 2018.

2.2 Sample Size Determination

Sample size was calculated using $n = \frac{2\,(Z\alpha+Z\beta)^2 s^2}{d^2}$, the formula for compa of groups [31];

where *'n'* is the minimum sample size, '*Zα'* is the significance level of 95% (with a value of 1.96), '*Zβ'* represents the power of 80 (corresponding to 0.84), '*S'* signifies standard deviation(SD) - the SD of the rate of healing of DFU using honey dressing from a similar study was 0.94 [32]*, while 'd'* is the level of precision (corresponding to 0.5).

Therefore, $n = \frac{2\,(1.96 + 0.84)^2\,(0.94)^2}{(0.5)^2} = \frac{2\,(7.84)\,(0.884)}{0.025} = 55.41$

To allow for an attrition rate of about 10%, the sample size was rounded up to 60 and adjusted for population <10,000 using the finite population correction (adjusted sample size) formula [31] where 'n_0' (minimum sample size) was 60, and 'N' (Total population of DFU in UPTH, 2016) was 47.

Therefore, the adjusted sample size = $\frac{n_0\,N}{n_0 + (N-1)} = \frac{60 \times 47}{60 + (47-1)}$ = 26.6 approximated to 30

Hence, a total sample size of 30 comprising of 15 patients per group were involved in the study.

2.3 Eligibility Criteria

The subjects were diabetics aged between 30-65 years (lower risk of co-morbidities) with Wagner Grade 2 foot ulcers.

2.3.1 Inclusion Criteria

They also met the following criteria:

a. Serum albumin concentration >35g/dl.

b. Oxygen saturation of ≥92% by pulse oximetry

c. Ankle-brachial pressure index (ABPI) >0.9,

2.3.2 Exclusion Criteria

Patients with severe immunosuppression, multiple co-morbidities, haemoglobinopathies, steroid therapy, neutrophil count < 2000/mm3. malignant disease or those receiving chemotherapy,

2.4 Study Procedure

2.4.1 Randomization

All subjects who consented to the study and met the inclusion criteria were randomized into two groups; Group A (honey group) and Group B (povidone iodine group) using an opaque envelope containing papers labelled either A or B. A paper was randomly drawn from the envelop for each eligible subject, who was assigned to the group label on the paper.

2.4.2 Blinding

The researcher was blinded to the dressing received, to avoid bias and ensure validity of the outcome measures. He was absent at the removal of old dressings, returned to measure the wound parameters, and left prior to the application of new dressings by trained nurses

2.4.3 Details of the Study

Honey was obtained from a single local source. Povidone iodine solution 10% was used in the control dressing group. All subjects received appropriate antibiotics and had surgical debridement by trained orthopaedic residents. Tissue specimens from the ulcer bed were immediately sent for microscopy, culture and sensitivity testing. Optimum blood glycaemic control was maintained under the supervision of a physician.

During dressings, the wounds were first cleansed with 0.9% saline, dressed with honey or povidone soaked gauze supported by layers of dry sterile gauze or Gamgee dressing, and then bandaged.

A weekly wound assessment was performed by the researcher who was blinded to the material of dressing, noting the wound contraction (the widest wound diameter in millimetres using a sterile tracing paper and meter rule), oedema regression (circumference of the foot midway between the tip of the big toe and heel, with a tape rule), characteristics of the exudate (serous, serosanguinous or purulent)

The assessment ended 6 weeks after the initial surgical debridement or when the wound had healed, whichever came earlier.

Plastic tape rules accurate to the nearest millimeter with a precision error of ±0.5mm were used. Parallax error was avoided. The measurements were done twice at each reading and the average taken. The research assistant was trained until an overall agreement of 90% between the researcher and the assistant was attained.

The consumables used include natural honey, 10% povidone iodine (Betadine®), normal saline, sterile cotton swabs, sterile gauze, crepe bandages, and sterile gloves.

STUDY PROTOCOL

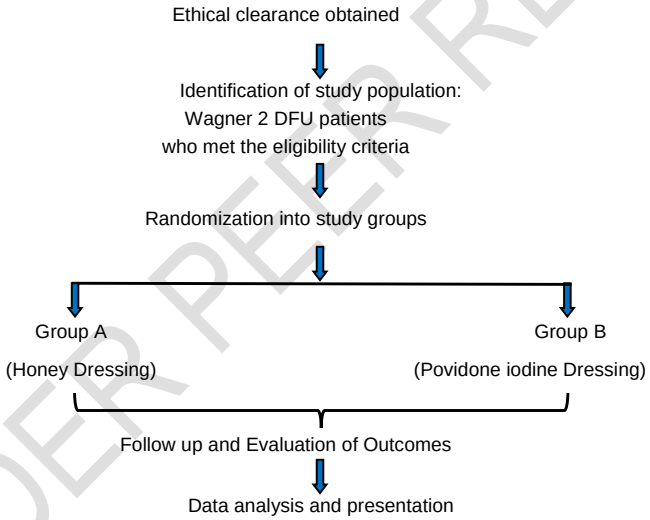

Figure 1: Diagrammatic Presentation of Study Protocol

2.5 Data Analysis

Data analysis was done using the statistical software package, IBM ® Statistical Package for the Social Sciences (SPSS) version 20. The data were presented as tables and charts. Qualitative variables such as age categories, sex and ulcer site were expressed as frequencies and proportions while quantitative variables such as ulcer diameter were summarized as means ± standard deviation. For data with normal distribution (such as ulcer diameter, MFC), the differences in means between the groups were compared using the student's t test. Chi square test or Fisher's exact test was used to compare the differences in proportions between the groups. A *P* value = 0.05 was considered statistically significant.

3. RESULTS

The study involved 17 males and 13 females (1.3:1 ratio). The honey group consisted of 8 (53.3%) males, while the povidone iodine group had 6 (40.0%) females. The participants were aged between 47 years and 65 years with a mean age of 55.53±5.041 years and 54.93±5.298 years for the honey and povidone groups respectively (t= 0.31; P= 0.75). There were no significant differences in the age (P=0.27) and sex (P=0.71) distribution between both study groups.

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Table 2: Demographic data of study participants

	Study Groups		
	Honey N=15	**Povidone Iodine N=15**	**Total N=30**
Variables	**n (%)**	**n (%)**	**n (%)**
Age category			
45-49 years	4 (26.7)	3 (20.0)	7 (23.3)
50-54 years	0 (0.0)	4 (26.7)	4 (13.3)
55-59 years	7 (46.7)	5 (33.3)	12 (40.0)
>60 years	4 (26.7)	3 (20.0)	7 (23.3)
	Fisher's exact test=4.432;P=0.27		
Sex			
Male	8 (53.3)	9 (60.0)	17 (56.7)
Female	7 (46.7)	6 (40.0)	13 (43.3)
	Chi-square=0.136;P=0.71		

The HbA1c values of the study subjects varied between 6.3% and 10.2% (mean: 7.40±0.944%) in the povidone iodine group, and from 6.7% to 9.9% (mean: 7.52±1.023%) for the honey group. This difference was not statistically significant (P=0.73).

Antibiotic powder was the most frequently utilised wound care product prior to hospital presentation (23.3%). Three patients (10%) used no products at all, whilst 13.3% used several. There was no significant difference between the two study groups (P=0.66) as shown in Table 3.

Table 3: Range of wound care products applied prior to hospital presentation

Products applied	**Study Groups**					
	Honey		**Povidone-Iodine**		**Total**	
	N=15	**n (%)**	**N=15**	**n (%)**	**N=30**	**n (%)**
Antibiotic powder	3	(20.0)	4	(26.7)	7	(23.3)
Cetrimide	1	(6.7)	3	(20.0)	4	(13.3)
Iodine	1	(6.7)	3	(20.0)	4	(13.3)
Hydrogen peroxide	2	(13.3)	1	(6.7)	3	(10.0)
Gentian violet	2	(13.3)	1	(6.7)	3	(10.0)
Eusol	2	(13.3)	0	(0.0)	2	(6.7)
Combined products	3	(20.0)	1	(6.7)	4	(13.3)
Nil	1	(6.7)	2	(13.3)	3	(10.0)
Total	**15**	**(100.0)**	**15**	**(100.0)**	**30**	**(100.0)**

Fisher's exact test=5.846; P=0.66

The widest diameters of the ulcers in this study ranged from 32mm to 51mm at baseline. The mean ulcer diameters were 42.9±4.9mm and 41.2±5.2mm for the honey and povidone iodine groups respectively after the initial debridement, and then 2.3 ±20mm and 4.7 ±8.0mm for the honey and povidone iodine groups respectively in the fourth week. Only one

diabetic patient under the povidone iodine group had an ulcer persisting from the fifth till the sixth week with an ulcer diameter size of 20mm by the fifth week, and 10mm by the sixth week as illustrated in Figure 2.

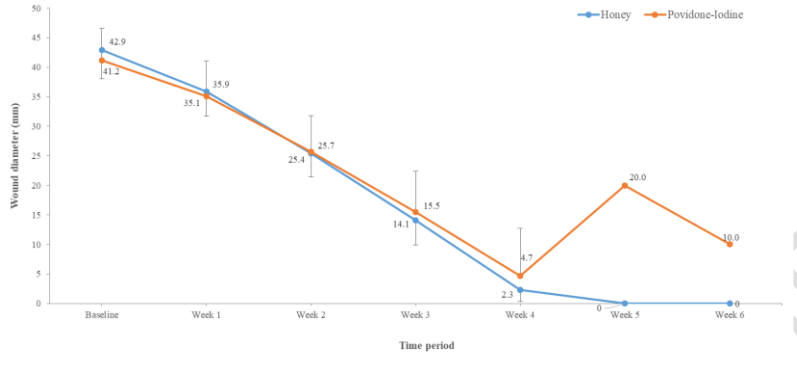

Figure 2: Error bar showing reduction of the mean (and standard deviation) ulcer diameter over time.

The mean change in ulcer diameter was -0.69±0.17mm and -0.61±0.11mm for the honey and povidone iodine dressing groups respectively (P=0.07) in week 1, and -0.23±0.41mm and -0.46±0.72mm for the honey and povidone iodine dressing groups respectively (P=0.11) in the week 5. There were no significant differences in the mean change in ulcer diameter between groups across the different time period as depicted in Table 4.

Table 4: Comparison of mean change in ulcer diameter during the follow-up period

	Study Groups			
Follow-up period	**Honey Mean change in ulcer diameter ± S.D (mm)**	**Povidone Iodine Mean change in ulcer diameter ± S.D (mm)**	**t**	**p-value**
Week one	-0.69±0.17	-0.61±0.11	1.514	0.062
Week two	-1.05±0.11	-0.94±0.13	2.495	0.838
Week three	-1.13±0.13	-1.01±0.16	2.225	0.581
Week four	-1.17±0.19	-1.08±0.16	1.482	0.124
Week five	-0.23±0.41	-0.46±0.72	1.051	0.112
Week six	-	0.10±0.00	-	-

S.D – Standard- Deviation

None of the respondents in both groups achieved complete wound healing in the first three weeks of follow-up. By week 4, 11(73.3%) and 6 (60.0%) had complete wound healing in honey and povidone iodine groups respectively. By week 5, all diabetic patients in honey group had complete wound healing while all but one of the patients in the povidone-iodine group had complete wound healing. The remaining lone DFU persisted till the end of the study period in week 6. This is shown in Figure 3.

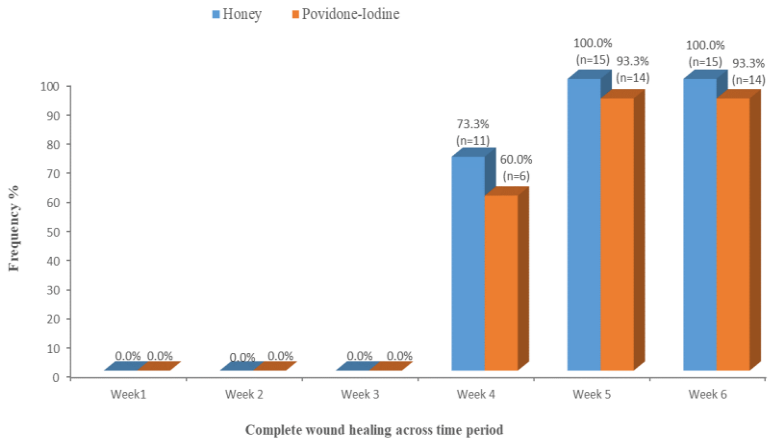

Figure 3: Distribution of patients with complete wound healing across the time period.

The mean change in mid-foot circumference (MFC) was -0.62±0.52cm and -0.29±0.35cm for the honey and povidone iodine groups respectively (P=0.05), by the second week. By the third week, there was little change the mid-foot circumferences, giving the mean reduction in mid-foot circumference of 0.00±0.04 and -0.02±0.08 for the honey and povidone iodine groups respectively (P=0.21). In week 4, there was no mean change in the mid-foot circumferences in both groups in the study. For weeks 5 and 6, only one DFU patient was remaining with change in the mid-foot circumferences of 0.50cm and -0.50cm in the respective weeks of follow-up as shown in Table 5.

Table 5: Comparison of mean change in MFC across groups during the follow-up period

	Study Groups			
Follow-up period	**Honey Mean change in MFC size ± S.D (cm)**	**Povidone Iodine Mean change in MFC ± S.D (cm)**	**t**	**p-value**
Week two	-0.62±0.52	-0.29±0.35	-2.034	0.051
Week three	0.00±0.04	-0.02±0.08	1.297	0.205
Week four	0.00±0.00	0.00±0.00	-	-
Week five	-	0.50	-	-
Week six	-	-0.50	-	-

S.D – Standard Deviation

In week 1, seropurulent exudates were noted on 6.7% of ulcers in each group, while serosanguinous exudates were seen on 66.7% and 60% of ulcers in the honey and povidone iodine groups, respectively. Serous exudates in the povidone iodine and honey groups were 33.3% and 26.7%, respectively. By week two, the povidone iodine group had 73.3% of ulcers with serous exudates, whereas the honey group had 66.7% of ulcers with serous exudates. However, during the third week, all of the exudates became serous, and they remained that way until the ulcers healed or the study was concluded as seen in Table 6.

Table 6: Wound exudate progression.

Week	**Exudate form**	**Study Groups**					
		Honey		**Povidone iodine**		**Total**	
		N=15	**n (%)**	**N=15**	**n (%)**	**N=30**	**n (%)**
1	Serosanguinous	10	(66.7)	9	(60.0)	19	(63.3)

	Seropurulent	1	(6.7)	1	(6.7)	2	(6.7)
	Serous	4	(26.7)	5	(33.3)	9	(30.0)
2	Serous	10	(66.7)	11	(73.3)	21	(70.0)
	Serosanguinous	5	(33.3)	4	(26.7)	9	(30.0)
3	Serous	15	(100.0)	15	(100.0)	30	(100.0)
4	Serous	4	(26.7)	6	(40.0)	10	(33.3)
5	Serous	0	(0.0)	1	(6.7)	1	(3.3)
6	Serous	0	(0.0)	1	(6.7)	1	(3.3)

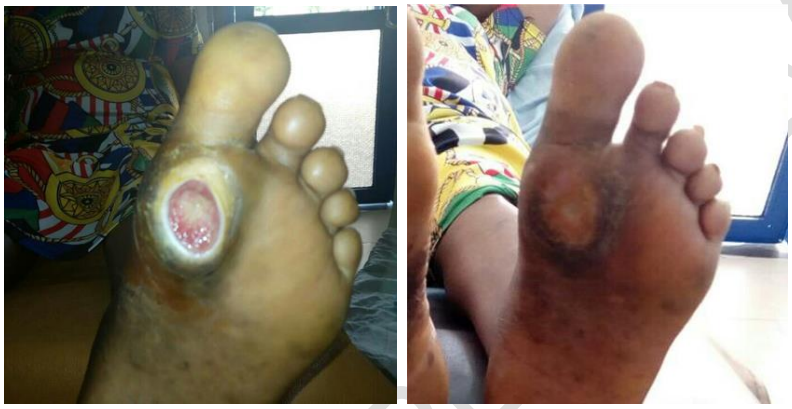

Figure 4: Plantar ulcer at (a) Week 1 (b) Week 4

4. DISCUSSION

The subjects who met the inclusion criteria were projected to have near-normal wound healing potential as possible. The rarity of this category of patients highlights the burden of diabetic complications including DFU, and implies that majority of diabetics may already have impaired healing capability at the time of presentation with DFU.[4][6][11] This fairly early presentation was possibly borne out of the health education obtained at the out-patient clinic. This perhaps enabled them to meet the stringent inclusion criteria as afore outlined, in contrast to the clinical and laboratory parameters of patients in other similar studies involving all grades of DFU. [33][34] Remarkably, Ogbera *et al*.[10] observed that 78% of their study respondents believed that 'poisoning' and 'curses' were responsible for foot ulcers, and thus were inclined to seek spiritual help before presenting to the hospital, a trend still often observed in the authors' practice. This necessitates improved efforts in patient and community education.

Both study groups had comparable demographic characteristics, HbA1c levels, and ulcer duration, thus excluding these parameters as confounding factors to wound healing. [11] [35]

In the honey group, foot ulcers with prior cetrimide, iodine and hydrogen peroxide treatment, or those untreated before debridement demonstrated an average healing time of 4.00±0.00 weeks. Similarly, ulcers in the povidone iodine group, previously treated with hydrogen peroxide, iodine, and gentian violet, took around 5.00±0.00 weeks to heal. The difference between the two groups was not significant, regardless of the specific wound care products administered prior to the study. This lack of distinction is likely because, before debridement, the ulcer sites contained varying amounts of slough, scab, and necrotic tissue, all of which were excised, resulting in fresh ulcer beds, probably unaffected by the previously applied substances. Additionally, progressive healing typically follows after debridement because the persistence of slough and necrotic tissue inhibit wound healing. [3][6][12][36]

The mean ulcer diameters were 42.9±4.9mm and 41.2±5.2mm for the honey and povidone iodine groups respectively after the initial debridement, and then 2.3 ±2.0mm and 4.7±8.0mm for the honey and povidone iodine groups respectively in the fourth week. This was because most of the ulcers had healed by then. The mean change in diameter of the ulcers was -6.9±1.7mm and -6.1±1.1mm for the honey and povidone iodine dressing groups respectively (p-value=0.062) in the first week, and -2.3±0.41mm and -4.6±0.72mm for the honey and povidone iodine dressing groups respectively (p-value=0.112) in the fifth week. The differences in means between groups were not significant all through the study period (p>0.05). This corroborates the findings of Shukrimi *et al,* [5] and Mohamed *et al.*[37] Equally, numerous studies reported the superiority of honey to produce faster healing, wound size contraction, and less pain than other conventional dressings owing to its unique properties.[8][14][34] Although advanced wound care technologies are being propagated as being more effective than honey, [4][12] they remain inaccessible in most developing countries.

The mean change in mid-foot circumference was -0.62±0.52cm and -0.29±0.35cm for the honey and povidone iodine groups respectively (p-value=0.051), by the second week. This was not found to be statistically significant. This corroborates the findings of other researchers and is believed to result from the high osmolarity via the absorption of the oedema fluid around the ulcer margins and anti-inflammatory properties of honey.[5][8][14] Oedema assessment with 3-dimensional (3D) imaging remains inaccessible in the developing world.[38] The mid-foot circumference is therefore recommended as a measure of foot oedema resolution or otherwise. A meticulous literature search found no record of evaluation of foot oedema by measurement of mid-foot circumference.

After the ulcers were debrided, serosanguinous exudates were first seen in over 63% of the ulcers. However, during the third week, every ulcer in both research groups developed serous exudates, indicating better healing. Exudates help to maintain the ideal moist environment for healing, offer antimicrobial protection, facilitate the movement of vital cells including macrophages and epithelial cells, and deliver nutrients and growth factors for cell metabolism and tissue regeneration. [39] Good exudate is typically serous (clear, pale amber, of watery consistency and odourless). [29][39]

The RCT design of this study, which endeavours to provide important information on the effect of honey versus povidone iodine on the pace of DFU healing, is one of its strongest points. Since a single-center study may limit the study's generalizability, multi-center studies are therefore recommended.

CONCLUSION

DFU present a number of problems that must be overcome for healing to progress. Although honey was marginally more efficacious, both honey and povidone iodine dressings show encouraging results in supporting wound healing and foot oedema control with no significant difference the two groups. Additionally, the type of exudates that an ulcer produces can be used as a marker for ongoing events. These findings call for more research and clinical consideration.

CONSENT AND ETHICAL APPROVAL

Ethical approval was obtained from the research and ethics committee of the UPTH before the commencement of the study. Written informed consent was obtained from all study participants after being given adequate information on the nature, scope, and reason for the research. Anonymity and confidentiality were upheld in the study. Participation in the study was voluntary, and patients' withdrawal from the study did not affect their medical care.

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