



Superior wound healing efficacy of Aloe Vera leaf gel extract dressings in diabetic foot ulcer

Manisha Singh Jadaun^{*1}, Senthil Kumar Muthusamy², G.B.K.S. Prasad², B.R. Shrivastava³

¹Department of Surgery, Gajra Raja Medical College, Gwalior (India)

²School of studies in Biochemistry, Jiwaji University, Gwalior (India),

³Cancer Hospital Gwalior (India)

*Corresponding Author E Mail id: drmanishasingh17@gmail.com

ABSTRACT

Diabetic foot ulcer is a serious complication and need early diagnosis with appropriate management to prevent non healing ulcer and amputations. Natural products like topical application of aloe vera are effective in healing wounds without adverse effects. To evaluate the effect of aloe vera gel extract in diabetic foot ulcers in terms of wound healing efficacy and time to heal the wounds. A prospective, randomized, case control study. We recruited 80 Type 2 Diabetes mellitus (DMT2) study participants (40 cases, 40 control) by convenience sampling to study the effect of topical aloe vera gel v/s saline on Diabetic Foot Ulcer (DFU) for 90 days. Base line characteristics such as mean age, gender, Body Mass Index (BMI), Neuropathy, ABI, Duration of DMT2, Lipid, Renal, Liver profile, signs/symptoms, and Random Blood Sugar (RBS) were comparable in the two groups. Mean RBS and mean wound area was found to be reduced gradually. Percentage wound contraction on 60th day was more in aloe vera group. Healing time was 80.2±16.1 days in aloe vera group v/s 89.3±21.0 days saline group. Aloe vera dressings were effective in terms of wound contraction and reduction of healing time compared to normal saline dressings in DFU

Key words: Aloe vera, saline dressings, wound contraction, Diabetic foot ulcer (DFU), Wound healing time, Random blood sugar, DMT2.

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INTRODUCTION

Difficult to heal wounds, susceptibility for infection, prolonged treatment time, danger of limb loss, pose a huge challenge to surgeons while managing diabetic foot wounds. Prevalence of diabetic ulcers is 6.3% across the world, 11.6% in India and account for majority of hospitalization in diabetic individuals [1]. Autoimmune insulin deficiency and insulin resistance result in hyperglycemia, increased oxidative stress, recurrent microbial infections and vascular insufficiency which contribute to chronicity of wounds [2-3]. In diabetics there is growth factor deficiency in wound medium which creates inflammatory stress by generating reactive oxygen species (ROS) with consequent elevated levels of interleukin-1Beta and tumour necrosis factor (TNF-alpha) [4-8]. Addition of growth factors kick-starts healing process in so called stalled chronic diabetic wounds by their stimulatory effect on local wound environment [9].

Natural products are more biocompatible, biodegradable, safe, nontoxic, rich source of antioxidants and enhance wound healing [10]. Choice of wound dressing in diabetic wound healing is associated with ability to maintain moist wound environment balance [11].

A medicinal herbaceous perennial plant aloe vera (*Aloe barbadensis*) plant gel is composed of several minerals, aminoacids, vitamins and water which help maintain moisture balance, stimulate cellular proliferation, improve collagen proliferation and accelerate wound healing [12-14].

Its wound healing efficacy has been proven in many studies and has been used in ancient traditional medicines for skin disorders [15]. Following topical application, increase in hyaluronic acid and dermatan sulphate content of granulation tissue has been reported [16]. Use of aloe vera leads to an overall reduction in inflammation on account of hydrolysis of bioactive molecules like prostaglandins, bradykinin, carboxypeptidase and brady kinase, in a healing diabetic wound [17].

Aloe vera has mannose rich polysaccharide compound Glucomannan and gibberellin a plant hormone which interact with growth factor receptors of fibroblasts to stimulate activity and proliferation leading to increase in collagen production post topical application. It also alters collagen composition (type III),

increases extent of collagen cross linking, helps wound contraction and potentiates tensile strength of scar tissue [18].

Its chemical constituents like mannose -6-phosphate help wound epithelialisation, acemannan a polysaccharide upregulates white blood cell activity and anthraquinones exert anti-bacterial activities [19].

MATERIAL AND METHODS

A randomized, case control, single blinded, prospective experimental study was conducted at Department of General Surgery, Gajraraja Medical College and JA group of Hospital Gwalior (M.P.) & Gwalior Diabetes & Foot Care Centre from June 2016 to Dec 2020.

Total 80 consecutive cases of diabetic foot ulcer were recruited by convenience random sampling and assigned to aloe vera, saline treatment groups after meeting inclusion and exclusion criteria.

Permission from Institutional Ethical committee was obtained (No. 22866-68). On the first visit, informed consent of the patients was taken, anthropometric measurements were recorded and general assessment of patients with neurovascular assessment of lower limbs along with foot ulcer examination were carried out. Total leukocyte count, Renal function tests, Liver function tests, Blood glucose, Glycosylated Hemoglobin (HbA1c), Fasting lipid profile, Procalcitonin, CRP level, were ascertained, X ray of foot and ECG were done.

Necessary instructions regarding offloading the ulcer and home/clinic dressings were given. In our study we used inexpensive offloading techniques such as walker, Rocker bottom shoes made by local cobbler and diabetic sandals (open Velcro belt sandals from markets). Neuropathy assessment (Biothesiometer, Monofilament test) was done along with test for Limited joint mobility (LJM), Ankle brachial index (ABI) and plantar pressure measurement (using Harris ink mat).

Inclusion criteria	Exclusion criteria
- Patients (type 2 DM) with diabetic foot ulcer - DFU Classified (UT classification) grade (1-2) stage (B) - Participating willingly in the study. - Male, Female; age range 20-80 years. - Emergency diabetic limb surgical intervention needed - Presence of diabetic neuropathy and retinopathy	- Poor general condition, not fit for anaesthesia and surgery. - Patients with ABI index < 0.9, PAD such as thromboangitis obliterans, Raynaud's disease, DVT and varicose veins. - Psychiatric illness. - Non-diabetic patients with foot ulcer - Deranged renal functions, osteomyelitis. - Coagulation disorders

Procurement and preparation of Aloe vera extract dressings

Fleshy leaves of aloe vera were identified and collected locally from School of Studies in Biochemistry, Jiwaji University, Gwalior and they also generously agreed to prepare and donate aloe vera extract powder and ointment for the study as method was already standardised in their laboratory [20,21]. Sterilization of ointment was done by UV rays at 254 nm light for 15 min [22].

Aloe vera gel extract ointment (10%) was used for application to diabetic foot wounds [23-24].

Composition of Aloe vera Gel extract

Ingredients	Quantity in 100 gm
Aloe vera Leaf Gel Extract	10%w/w
White soft Paraffin	90%w/w

Estimation of antioxidants in wound tissue:

Superoxide dismutase was assayed as per the method described by Winterbourn (1993). Catalase estimation was done as per Aebi (1984) and Gutathione estimation was based on reduction of 5,5-dithio bis (2-nitro benzoic acid) according to Ellman, (1959) [25-27].

Identification of microbes harbouring wound tissue:

Deep tissue specimens subjected to microbial culture for identification of bacterial species harbouring the deep wound tissue and their antibiotic sensitivities by classical methods.

Histopathological observation of the wound tissue

The tissue biopsy from the wound was collected once before the commencement of treatment and at the end of 60th day of treatment and was subjected to histological examination.

Experimental design

Classification of the wound was done as per University of Texas classification system of diabetic foot. According to the experimental design, the day of first debridement after recruitment was considered day zero (0), then subjects were randomly divided into two equal groups of Forty each.

1. Control group (kept on standard normal saline dressings) - 40 cases

2. Experimental group (kept on topical Aloe vera gel application) - 40 cases

Aloe vera gel / ointment and normal saline were used as treatment dressings for the diabetic foot wounds.

Broad spectrum antibiotics (injectable) were administered to subjects of both the groups on first visit followed by culture specific antibiotic later. Insulin and oral hypoglycemic drugs were given for glycemic control.

Experimental Procedure – this involved three main steps

1. Thorough foot lavage before applying treatment.

2. Debridement (sharp) of necrotic tissue (in operation theatre / ward) to promote healthy tissue granulation, sending deep tissue sent for culture sensitivity and biopsy from the edge of ulcer (Biopsy I).

3. Applying primary treatment dressings (aloe vera/normal saline) to the ulcer followed by secondary dressings and crepe bandage.

Dressings changes were done daily / alternate day / as per requirement and offloading advised for plantar ulcers.

Wound dimensions: Wound outline was traced on transparent plastic paper with wound area being determined on graph paper at days 0, 10th day, 20th day 30th, 40th, 50th 60th 70th, 80th, 90th and 100th day.

Full thickness wound biopsy including small portion of normal skin was taken from edge of the wound on day 0 and 30th day for histopathological examination.

Complete healing was defined as complete epithelialization of the wound.

RESULTS

The study included both males 71.25% (N=57) and females 28.75% (N=23) with overall mean age observed to be 56.09 years and there was no significant difference between two study groups.

Table 1: Frequency and percentage distribution of Age and Gender of the subjects in two study groups

Study Group	Number of subjects	Mean age	Std. Deviation	BMI kg/m ²		Blood Pressure mmHg			
						SYS		DYS	
				Mean	SD	Mean	SD	Mean	SD
Aloe vera	40 (30,10)	55.1	13.1	29.7	3.8	141.7	9.0	82.9	9.2
Saline	40 (27, 13)	57.08	9.4	28.1	5.3	140.8	15.1	80.9	9.5
Total	80 (57,23)	56.09	11.2	28.0	4.55	141.2	12.0	81.9	9.3

Values are expressed in Mean±SD, * p value p<0.05.

We ascertained the basic and anthropometric parameters of the study population, mean age being 55.1 years in aloe vera group and 57.08 years saline study group. In both groups maximum patients were (Aloe vera =20, Saline =24) in the age group 41-60 years and no significant difference was found between study groups based on age. Mean BMI was found to be 29.7 kg/m² in aloe vera group and 28.12 kg/m² in saline group. The mean Systolic BP was 141.7 mmHg and 140.8 mmHg in aloe vera and saline group respectively and these values were found to be significantly different (p= < 0.05). Diastolic BP was found to be 82.9 mmHg and 80.9 mmHg in aloe vera and normal saline group respectively, but no significant difference was found between study groups based on Diastolic BP (p=0.89).

Table 2: Glycaemic parameters and lipids profile in subjects of different study groups

Study Group	RBS		HbA1c %		C-peptide		T. Cholesterol		Triglycerides mg/dl		HDL-Cholesterol mg/dl	
	mg/dl				ng/ml		mg/dl					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Aloe vera	268.4	33.5	7.72	0.99	1.84	0.64	214.6	58.5	173.8	26.6	49.7	4.9
Saline	275.5	68.8	7.8	0.75	1.65	0.78	206.8	39.4	196.6	44.6	45.5	5.1
Mean of Total	271.95	51.15	7.76	0.87	1.745	0.71	210.7	48.95	185.2	35.6	47.6	5

Note: Values are expressed in Mean±SD, * p value $p < 0.05$.

No significant variations between the two study groups were recorded in case of glycemic parameters but statistically significant variations ($p < 0.05$) were recorded in case Total cholesterol, Triglycerides and HDL Cholesterol.

Table 3: Liver function and Renal function profiles among study participants in different study groups

Parameter		Aloe vera	Saline	Mean of all subjects
SGOT (IU/l)	Mean	55.2	56.7	55.95
	SD	16.7	11.4	14.05
SGPT (IU/l)	Mean	56.4	57.5	56.95
	SD	17.4	12.6	15
S. Bilirubin (mg/dl)	Mean	1.5	1.7	1.6
	SD	0.65	0.72	0.685
PT (min)	Mean	12.2	12.4	12.3
	SD	0.85	0.88	0.865
Urea (mg/dl)	Mean	40.2	39.5	39.85
	SD	9.8	9.6	9.7
Uric acid (mg/dl)	Mean	5.8	5.6	5.7
	SD	1.1	1.2	1.15
Creatinine (mg/dl)	Mean	1.3	1.3	1.3
	SD	0.8	0.9	0.85
S. Na ⁺ (mEq/L)	Mean	135.1	136.9	136
	SD	5.3	6.2	5.75
S. K ⁺ (mmol/L)	Mean	4.9	4	4.45
	SD	0.3	0.5	0.4

Complete liver function and Renal function profile markers were monitored in all subjects but no significant difference was found between two groups.

Table 4: Tissue antioxidants levels in study subjects.

Study Group	SOD (U/min/mg protein)		GSH (U/min/mg protein)		Catalase (U/min/mg protein)	
	Mean	SD	Mean	SD	Mean	SD
Aloe vera	34.8	5.3	0.72	0.24	5.5	2.6
Saline	39.3	8.9	0.8	0.24	5.7	2.7
Mean values of both groups	37.05	7.1	0.76	0.24	5.6	2.65

Tissue antioxidants levels of subjects although raised initially but were not significant in different treatment groups and the levels reduced once mean wound area started reducing.

Table 5: Neutrophils / lymphocytes count in aloe vera / normal saline treatment groups.

	Neutrophils count			Lymphocytes count		
	0 days	30 th days	60 th days	0 days	30 th days	60 th days
Aloevera	84	74	62	12	19	26
Saline	81	71	60	15	23	29
Mean values of both groups	82.5	72.5	60	13.5	21	29

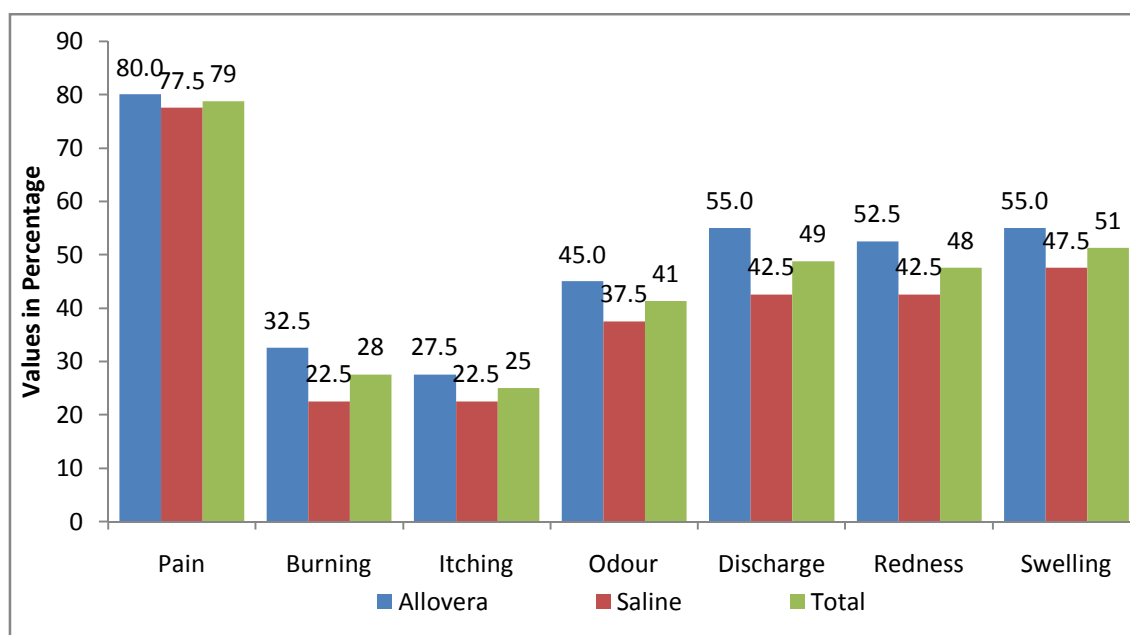
Mean neutrophil/lymphocyte ratio in

Aloe vera group – **8.4** Day 0; **4.9** Day 30 : **2.2** -Day 60,

Saline group– **6.6** Day 0; **3.8** Day 30 : **2.2** -Day 60

Table 6: Signs and Symptoms of the study subjects in different treatment groups.

	Pain	Burning	Itching	Odour	Discharge	Redness	Swelling
Aloe vera	80.0	32.5	27.5	45.0	55.0	52.5	55.0
Normal saline	77.5	22.5	22.5	37.5	42.5	42.5	47.5

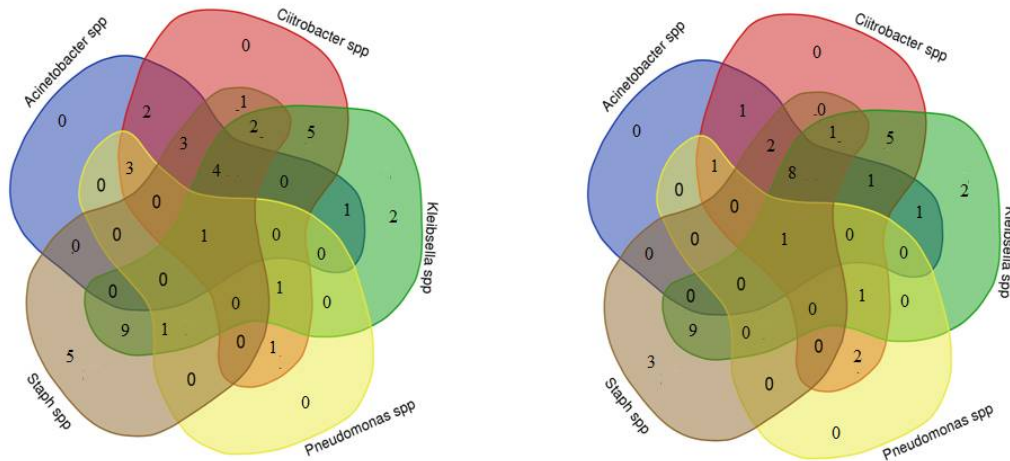
**Figure 1: Signs and Symptoms of the study subjects in different treatment groups.**

In our study overall subjective symptoms like pain (79%), burning (28%), Itching (25%) were reported by the study subjects and the signs observed in ulcer area were odour (41 %), discharge (49 %), redness (48 %) and swelling (51%).

Isolation of wound pathogens from deep tissue specimens obtained from study subjects. Deep tissue specimens subjected to microbial culture for identification of bacterial species harbouring the deep wound tissue and their antibiotic sensitivities.

Kleibella pneumoniae, *Pseudomonas aeruginosa*, *Acinetobacter lwoffii*, *Staphylococcus aureus*, *Staphylococcus similis*, *Citrobacter frundi*, *Citrobacter sedlakii*, were isolated from wounds of the study subjects.

Upto two species of pathogen were found in 52.5% cases in aloe vera group and 47.5% in saline groups.



Figures 2:Pattern of polymicrobial infections in study subjects.

Frequency and percentage distribution of Poly microbial infection among the study participants based on treatment

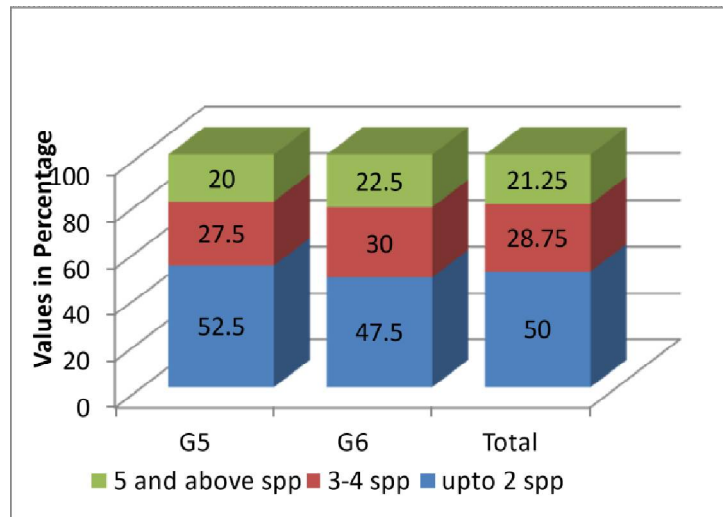


Figure 3: Poly microbial infection with percentage distribution of number of pathogens species in various treatment groups.



Figure 4: Comparison of percentage wound contraction on 60th day among various Treatment groups (p=value<0.05).

Wound area during the follow-up in different treatment groups,

Wound healing is measured as a contraction of the wound area as mentioned in the Fig 5. the follow-up found reduction in the wound area, with maximum contraction at 60th day and by 90th day, all most all the wound was cured. The wound areas from two different dressings were plotted against days.

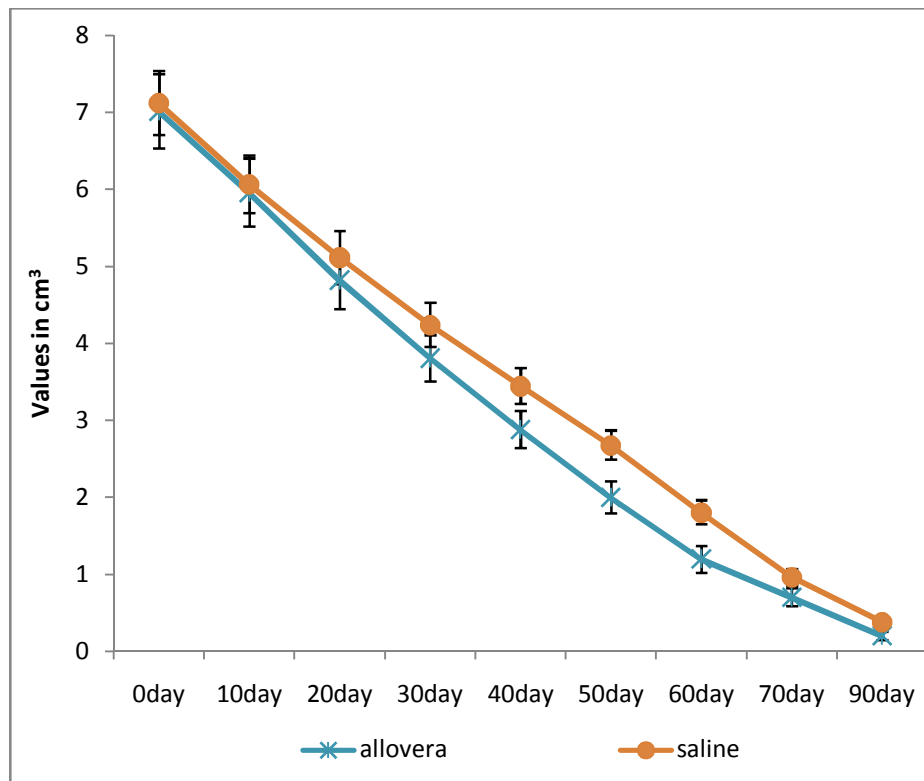
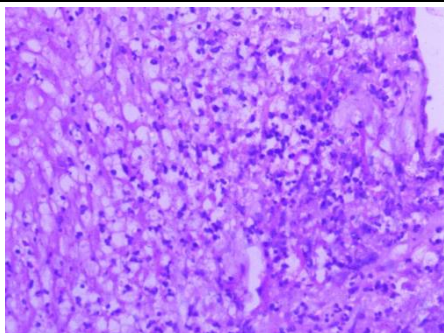


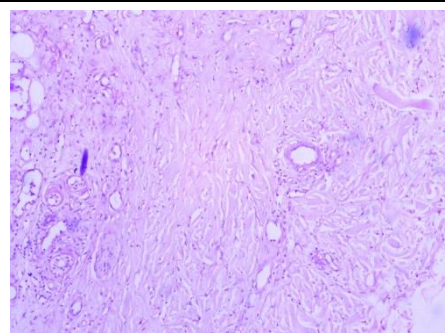
Figure 5:Wound area during the follow-up in different treatment groups,

Table 7: Frequency and percentage distribution of study subjects in various treatment groups on the basis duration of ulcer healing.

S.No	Treatment	N	Mean (days)	Std. Deviation
1	Aloe vera	40	80.2	16.1
2	Normal Saline	40	89.3	21.9



Aloe vera Day 1st
(40 X High power showing inflammation & edematous tissue)



Aloe vera Day 30th
(10X Low power showing collagenised tissue with few congested capillaries)

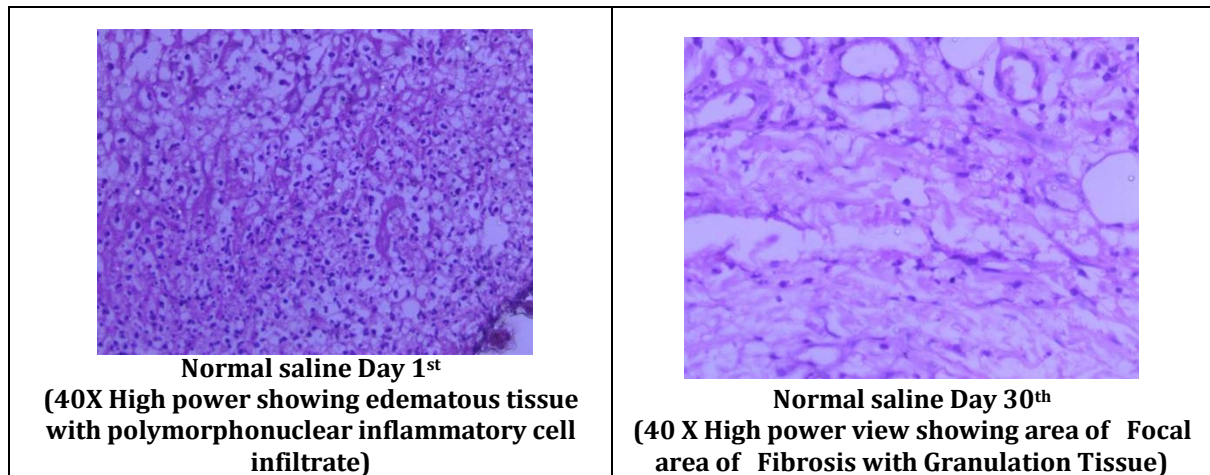


Figure 6: Histopathological observation of the wound tissue.



Figure 7: Images of wound during the course of treatment.

DISCUSSION

The cellular and molecular mechanisms involved in healthy acute wound healing are clear to a larger extent now. A small cut generally will heal in days through tight orchestration of cell migration and appropriate levels of inflammation, innervation and angiogenesis. Chronic wounds in diabetic subjects may take weeks to months' time to heal and may leave a noticeable scar. Thus, chronic wounds in diabetic subjects have become a major therapeutic challenge to the surgeons across the globe although there are several developed wound dressing materials for the management of acute and chronic wounds. There is considerable overlapping in the three phases of normal wound healing viz., inflammatory, proliferative and maturation phases [28].

In our study on type II diabetic subjects, there was predominance of clinical symptoms and signs of inflammation such as pain, redness, discharge, swelling and foul odour before treatment. In less than a week, these signs disappeared more rapidly in aloe vera group.

A high neutrophils/lymphocytes ratio (NLR) represent dysfunction of endothelium due to neutrophils over activity. Value of neutrophils / lymphocytes ratio (NLR) complete healing and is an indicator of infection and severity [29-31]. The neutrophils count reduction accelerates re-epithelialization. There were elevated neutrophils count on day 0 (initial visit) which declined significantly on 30th and 60th day so as neutrophils / lymphocytes ratio (NLR) which showed gradual decline with the wound contraction (healing). A significant rise in neutrophils and lymphocyte count at inflammatory phase and fall in proliferative and maturation phases of wound healing was found in an earlier study on application of aloe vera gel in wound of rabbits 90 [32]. A mixed bacterial flora was recorded in deep tissue, *Staphylococcus aureus*, *Klebsiella* being predominant isolates. Presence of phenols, saponins and anthraquinones in aloe vera are responsible for antibacterial activity which might have helped in clearing infection and progress of healing after topical application.

Application of Aloe vera as a medicinal plant for skin wound healing is confirmed and its wound related therapeutic spectrum is due to antibacterial, anti-viral, anti-inflammatory effects [33,14]. Dat and colleagues (2012) showed that Aloe vera is more effective in chronic than acute wounds [34].

Presence of phytochemicals such as flavonoids and saponins have antioxidant effect too and are found useful in protecting and repairing damaged tissue of plants and animals. Tissue catalase, Superoxide dismutase activities were found to decrease progressively with treatment in our study and may be due to local antioxidant effect of aloe vera. Gibberellin a growth hormone and glucomannan, a mannose-rich polysaccharide in Aloe vera gel interacts with growth factor receptors to stimulate proliferation of fibroblasts and collagen synthesis [35-37].

Comparative analysis of wound healing kinetics in the two treatment groups revealed superiority of aloe vera dressing compared to saline based dressing. The percentage contraction was maximum on 60th day in aloe vera group compared to saline group. The mean wound healing time was 80.2±16.1 days and 89.3±21.9 days in aloe vera and saline (control) groups respectively.

Positive effect of topical application of aloe vera has also been studied in open wounds by evaluating molecular and cellular activity of fibroblast cells and TGF-Beta expression [38] and thus the superior wound healing effect of aloe vera dressing may also be due to its TGF β expression potential besides its anti-bacterial potential. Acemannan (major carbohydrate fraction), phenols, saponins, anthraquinones are present in significant amounts in aloe vera which produce antiviral, antifungal, antibacterial activity to further stimulate immune system, macrophages, and wound healing [39]. It is reported that Acemannan produces enhanced angiogenesis due to VEGF, type 1 collagen production, in addition to boosted collagen synthesis and better wound health as found in oral wound healing [40-41].

Prohealing ingredients in aloe vera such as vitamins C, Amino acid, Vitamin E and zinc may be responsible for improved healing [42-45].

Topical application of Aloe vera prevents ulcers and enhances the healing process of dermal injuries and chronic wounds such as DFU (Joseph & Raj, 2010). It was more effective than petroleum jelly gauze dressing, silver sulfadiazine 1% ointment, and framycetin cream. Moreover, it reduced the recovery time, prevented infection in the wound area, and prevented redness and itching [45-46] and reduced the pain, bleeding, and recovery time in chronic wounds.

Another study conducted earlier showed that wound healing occurred in 28 (93.3%) of patients in the Aloe vera group and 14 (46.7%) patients in the control group ($P < 0.05$) after 3 months. The overall mean time of wound healing was 31.25±11.2 and 63.2±20.4 in the Aloe vera and control groups, respectively ($P < 0.05$) in their study [45]. Thus, the present study conducted on diabetic wound ulcers proved that aloe vera dressings could be used for faster healing of chronic wounds. The aloe vera dressings are cost effective and within the budget limits of general population.

CONCLUSION

Aloe vera dressings expediate wound healing to promote wound closure without any adverse reactions compared to saline dressings in diabetic foot ulcers.

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