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A RANDOMIZED CONTROL CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BIODEGRADABLE PATCH IMPREGNATED WITH COMPOUND AYURVEDIC DRUG IN MILD TO MODERATE INFECTED WOUND

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ABSTRACT

Objective: The present study was undertaken to assess the wound healing dermal patch as a dressing material using Compound Ayurvedic drug impregnated in a Poly(lactic acid) polymer as a biodegradable template in mild to moderate infected wounds. **Material and method**: Drugs were applied topically once a day in patients who were randomized into two groups; Group I was given Colloidal silver ointment, Group II was treated with Compound Ayurvedic drug impregnated in Biodegradable patch. Assessment of wound healing was based on criterias like Pain, Discharge, Slough, Surface area, Unit healing time and Histopathological study. All the above parameters were assessed on baseline, 7th day, 14th day & 21st day. **Conclusion**: Topical application of wound healing dermal patch (PLA-CAD) reduced pain, discharge, slough, surface area, and unit healing time of the surrounding tissue substantially in comparison to control group (MEGAHEAL).

KEYWORDS: biodegradable patch, clinical trial, infective wound, polymer,

INTRODUCTION

A wound is described as 'a break in the continuity of tissue, from violence or trauma' and is regarded as healed if there is a restoration of the wounded or inflamed tissue to normal Condition.[1] The global wound mortality rate is estimated to be 98/100,000 population, with male and female rates of 128/100,000 (38 lakh deaths) and 67/100,000 (19 lakh deaths), respectively (WHO). Worldwide prevalence of traumatic wounds occurs at a rate of about 1.6 million cases every year.[2] The prevalence of wounds in the population studied in India was 15.03 per 1000. The prevalence of acute and chronic wounds was 10.55 and 4.48 per 1000 of the population respectively[3] Percentage of wound in hospitalised patients is around 14.7%. In India, the attributable cost of wound care in 2006-2007 was 340 cores.[4]

Research on wound healing drugs is a developing area in modern biomedical sciences. Scientists who are trying to develop newer drugs from natural resources are looking towards the Ayurveda, the Indian traditional system of medicine. In the Indian traditional system of medicine, the formal descriptions of wound care have been vividly elaborated in three equal great treatises (Brihatrayi) of Ayurveda viz. *Charaka Samhita, Sushruta Samhita* and *Ashtang Sangraha*. Acharya Sushruta was perhaps, the first Surgeon who had for the first time in human history elaborated the concept of wound. He not only gave an elaborate description of various types of wounds but also presented a descriptive aetiopathogenesis of various types of wounds along with their management.[5] In Ayurveda, Sushruta told various drugs and preparations for the management of wound . Out of all these drugs some have wound debridement/wound cleansing properties and some other has wound healing properties.[6] It is nearly not possible to provide complete management by using single drug. So it is needed to use a poly herbal preparation for the management of infective wound, which have both wound cleansing and wound healing properties. The Compound Ayurvedic Drug consists aqueous extract of stem bark of four Ficus species of Vata (*Ficus bengalensis* Linn.),Ashwatha (*Ficus religiosa* Linn.),Udumbara (*Ficus glomerata Roxb.*),Plaksha (*Ficus lacor* Buch-Ham.).[7]

The drug delivery through Dermal patch has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolonged period of time.[8] Therefore the dermal patch technology has proven to be fastest, easiest, safest and most economical way to help wound to heal.[9] The use of polymeric materials in or as drug delivery devices involves incorporation of biodegradability into the

drug delivery system.[10] However, a number of degradable polymers are potentially useful for this purpose including a variety of synthetic and natural substances. Among these Poly (lactic acid) (PLA) has been used worldwide as bio degradable substrate for nano drug delivery.[11]So in this study Poly (lactic acid) (PLA) was used as a substrate for wound dressing material for impregnation of active ingredients of Compound Ayurvedic Drug.

Therefore the present study was planned to evaluate the Compound Ayurvedic Drug which includes aqueous extracts bark of Vata (*Ficus bengalensis*Linn.), Ashwatha (*Ficus religiosa*Linn), Udumbara (*Ficus glomerata*Roxb.), and Plaksha (*Ficus lacor*Buch-Ham) impregnated in a Poly (Lactic Acid) based biodegradable patch clinically for their possible wound healing effect on mild to moderate infective wound on clinical parameters.

MATERIAL AND METHOD

Preparation of Biodegradable Patch by Solvent Casting Method: In the present study aqueous extract of all four drugs (CAD) were together grinded and the powdered drug were put through sieve no. 100 to fix the particle size of drug to 100 micron. Poly (lactic acid) polymer was taken with Dichloromethane solution. 25%W/W Compound Ayurvedic Drug was mixed with dichloromethane solution and kept over ultrasonicator for dispersion. After ultrasonication 25%W/W Compound Ayurvedic Drug was mixed with polymer solution and kept over rotator having 1500rpm for mixing. Standard Film applicator was taken to make the film of a standard size of 100 micron thickness. The Solution of Compound Ayurvedic drug and Polymer was pasted over glass sheet in a cold room at 4°C. The Film applicator was moved over the solution and a film of 100 micron standard thickness was made. Dichloromethane, being a volatile substance got evaporated and Bio degradable film having 25% W/W drug and polymer remained in the patch. Biodegradable patch was finally made after evaporation of the solvent. The prepared films were peeled from the plates and the films showed good film forming property (filmogenicity).

CLINICAL STUDY

Selection of Cases: All the patients with mild to moderate infective wound were registered from Shalya OPD/IPD of Sir Sundarlal Hospital IMS, BHU, Varanasi. Random selection was made irrespective of age, group, sex, duration of wound sign-symptom and associated disease like diabetes, hypertension etc. including infected surgical wound were also registered. However, malignant ulcer excluded from the study.

History: A detailed history was taken from each patient like chief complain of patient with duration, mode of onset, and sequential changes take place in illness were also noted. Pain, discharge, edema, and associated diseases were noted. History of previous medical and surgical treatment, family history, occupation, personal history was also enquired and noted.

Systemic Examination

Systemic examination of each patient was done for cardiovascular, respiratory, digestive, nervous system and genito-urinary system, specific investigation of any system if required was carried out.

Local Examination

It was carried out under following heading

Inspection

1. Site of wound
2. Size
3. Shape - Oval/round/straight/other
4. Color - Yellowish/greenish/reddish
5. Base
6. Floor- Unhealthy granulation tissue/rad and healthy granulation tissue
7. Edge- Undermined/punched out/sloping/raised/rolled out
8. Margin- Thin/thick/irregular/inflamed
9. Discharge - Thick pus/blood/serous/frothy
10. Edema

Palpation

1. Local temperature-Raised/normal
2. Tenderness-Present/absent
3. Edge
4. Base
5. Depth
6. Induration
7. Extent of infection
8. Lymph node-Palpable/not palpable

Investigation

Routine

Hematological	TLC, DLC, Hb, ESR, blood urea, fasting and post prandial blood sugar.
Serum	Serum Creatinine, HIV
Urine	Routine and microscopic examination

Specific: Microbial load assessment.

Radiography: In suspected cases; Chest X-ray to rule out pulmonary tuberculosis and X-ray of wound site to rule out Osteomyelitis or any other bony lesion.

Selection of Patients: Present study was carried out in 36 cases of mild to moderate infective wound. These cases were randomly divided in two groups containing equal number of patients i.e., 18 patients in each group.

Group-1: 18 patients were taken and daily dressing was done by Colloidal Silver Ointment (MEGEHEAL).

Group-2: 18 patients were taken and daily dressing was done by Compound Ayurvedic drug impregnated in the Poly (Lactic Acid) (PLA) polymer.

Inclusion Criteria

1. Patient with the history of mild to moderately infective wound having microbial load in between 10^{5-} 10^{7}colony forming unit per 1 gram of tissue.
2. Diabetic ulcer (controlled blood sugar) regardless of sex, age or chronicity of disease.

Exclusion Criteria

1. Patient suffering from any type of malignancy
2. Leprotic wound
3. Uncontrolled diabetes
4. Patient in ARF or CRF
5. Patient in septicaemia
6. Tuberculosis
7. Immunocompromised patient.

Criteria for Assessment

1. Clinical features

A. Pain

B. Discharge

C. Slough

D. Surface area

E. Unit healing time

The included patient were assessed on the basis of following signs and symptom and subsequently patients were assessed for all the parameters from first visit and weekly henceforth at subsequent intervals *i.e.*0, 7, 14, 21, 28th day.

2. Measurement of wound

a) Linear measurement – Length, Width, Depth, Area

b) Tracing

c) Photography

d) Unit healing time

Grading for Pain (Evaluated on 0–3 scale)[12]

0 = No pain.

1 = 1-3 in the VAS, mild pain.

2 = 4 - 7 in the VAS, moderate pain.

3 = 8-10 in the VAS, severe pain.

Grading for Discharge (Evaluated on 0–5 scale)[13]

0 = No discharge / dry dressing.

1 = Scanty occasional discharge & little wet dressing.

2 = Often discharge & with blood on dressing.

3 = Profuse, continuous discharge which needs frequent dressing.

Evaluation of Slough (Evaluated on 0–5 scale)[14]

0 = No slough

1 = 20% wound surface covered with slough.

2 = 40% wound surface covered with slough.

3 = 60% wound surface covered with slough.

4 = 80% wound surface covered with slough.

5 = 100% wound surface covered with slough.

Surface area

Initial area –last area of wound (in sq. cm.)

Unit Healing Time (UHT)

Initial area – last area of wound (in sq. cm.) / Total number of days of treatment

Histopathological assessment

Histopathological changes were seen on the 7th day and 14th day of treatment.

Statistical analysis of pain in both groups.

The statistical analysis of Pain in both groups revealed that in Group I 1,9,5,3patients of 0,1,2,3 grade initially and after treatment in fourth followup15 patients (83%)were in 0 grade and 3 patients were in 1 grade. The statistical analysis of pain in both groups revealed that in Group I 0,4,8,6 patients of 0,1,2,3 grade initially and after treatment in fourth followup18 patients (100%)were in 0 grade.(Fig. No. 1)

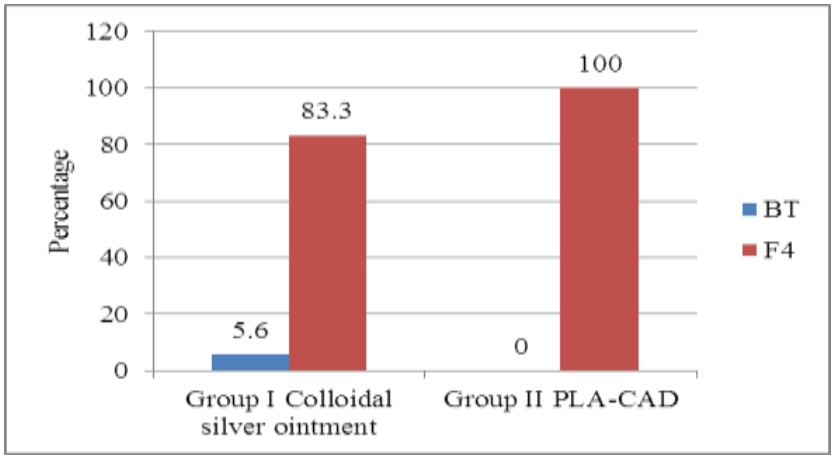


Figure No. 1

Statistical analysis of discharge in both groups.

The statistical analysis of discharge in both groups revealed that in Group I 1,6,7,4 patients of 0,1,2,3 grade initially and after treatment in fourth followup13 patients (72%) were in 0 grade and 5 patients were in 1 grade. The statistical analysis of discharge in both groups revealed that in Group II,6,7,4patients of0,1,2,3 grade initially and after treatment in fourth followup18 patients (100%) were in 0 grade. (Fig No. 2).

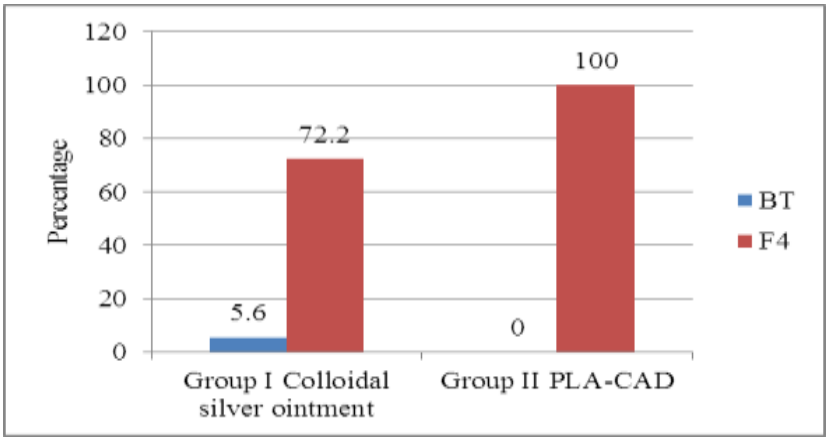


Figure No. 2

Statistical analysis of slough in both group

The statistical analysis of slough in both groups revealed that in Group I 3,4,4,3,4,0 patients of 0,1,2,3,4,5 grade initially and after treatment in fourth followup14 patients were in 0 grade(77%) and 4 patients were in 1 grade. The statistical analysis of slough in both groups revealed that in Group I 0,0,0,4,9,5 patients of0,1,2,3,4,5 grade initially and after treatment in fourth follow up 13 patients (72%) were in 0 grade and 5 patients were in 1 grade. (Fig. No.3).

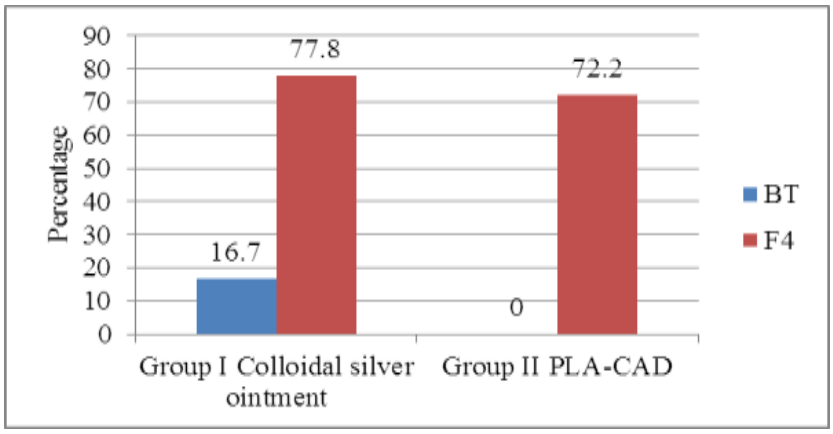


Figure No. 3

Statistical analysis of surface area in both groups

The statistical analysis of surface area in both groups revealed that in Group I initially mean was 31.94 ±18.18 and at first, second, third, fourth, fifth, sixth and seventh follow up it was 24.28 ±17.18, 16.82 ±16.19, 10.96 ±13.58, 6.37 ±10.18, 3.46±7.12, 1.36 ±3.87, 0.45 ±1.67. In Group II, initially mean was 36.91 ±22.11 and at first, second, third, fourth, fifth, sixth and

seventh follow up it was 28.08 ±21.59, 21.10 ±19.13, 15.21 ±16.31, 10.10 ±12.82, 5.99 ±9.13, 2.82 ±5.70, 1.03 ±2.42. (Fig. No. 4).

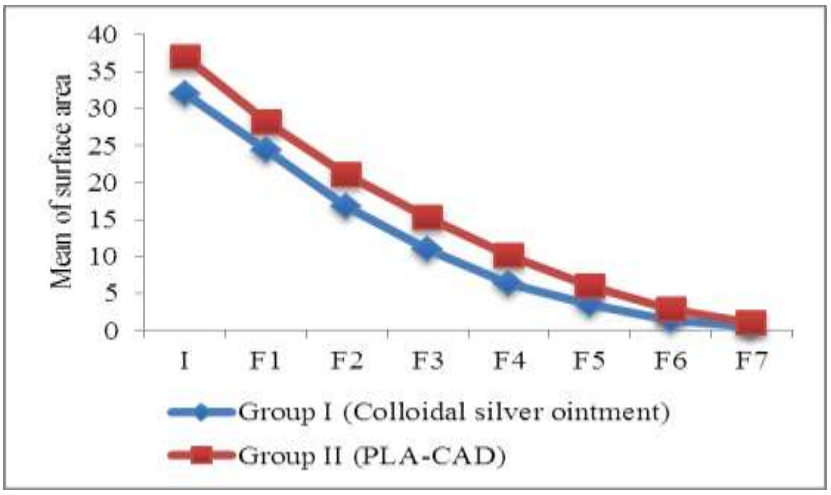


Figure No. 4

Statistical analysis of Unit Healing Time in both groups

The statistical analysis of Unit healing time in both groups revealed that in Group I initially mean was 0.967 ±0.102 and at first, second, third, fourth and fifth follow up it was 0.981 ±0.376, 0.686 ±0.450, 0.457 ±0.479, 0.326 ±0.485, 0.220 ±0.423.Mean difference between I-$F_4$was 0.6418± 0.5377.In Group II, initial mean 0.791 ±0.058 and at first, second, third and fourth and fifth follow up it was 0.555 ± 0.359, 0.517 ± 0.382, 0.380 ± 0.392,0.348 ± 0.403,0.168 ±0.324 and the mean difference between I-$F_4$was 0.4430±0.404 (Fig. No. 5).

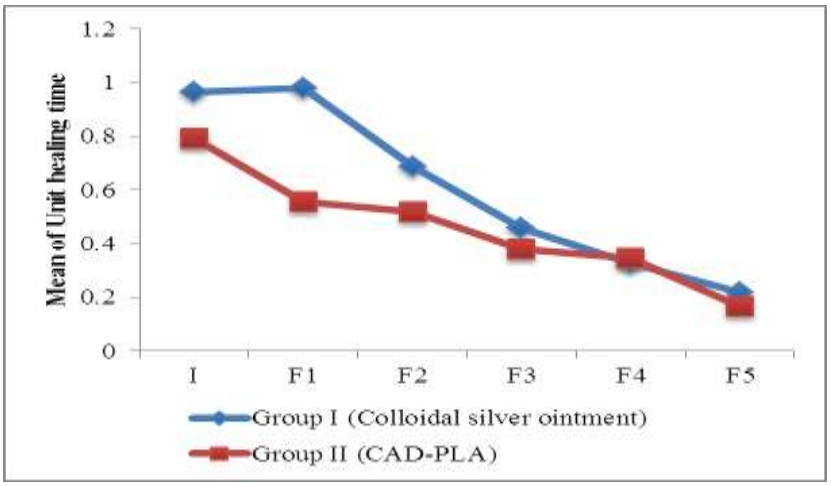
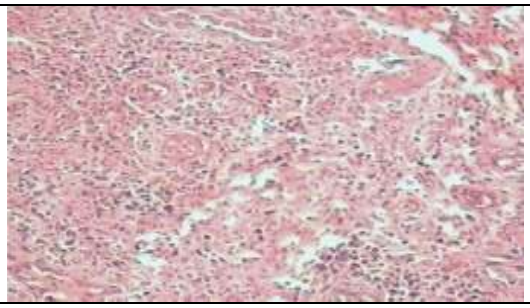
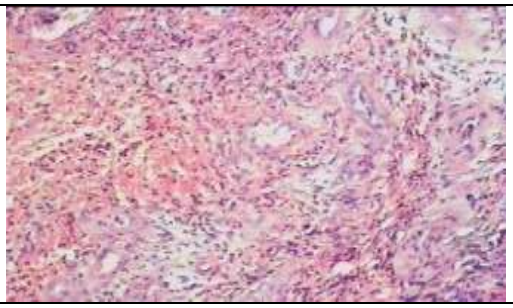


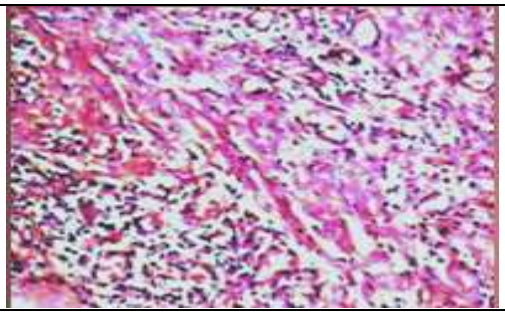
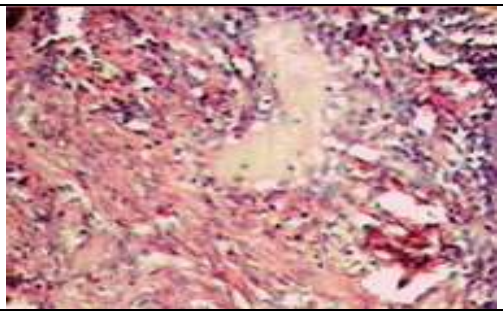
Figure No. 5

HISTOPATHOLOGICAL STUDY

7th day

	
Neutrophilic infiltration are more	**Inflammatory component are less collagen and lymphatic channel are present**

14th day

	
Collagen bundle present and neutrophilic infiltration are less	**Endothelial cell proliferation and collagen bundle**

HISTOPATHOLOGICAL RESULTS ANALYSIS

Day	Group I	Group II
7th day	Abundant polymorphs, presence of necrosis, microabscess, negligible granulation tissue, marked no. of inflammatory cell	Marked polymorphs, Marked microabscess,predominant inflammatory cells, marked necrosed tissue, negligible granulation tissue
14th day	Healthy granulation tissue, few microabscesses, chronic inflammatory cell, improved collagen laying	Absence of polymorphs and necrosed tissue, less inflammatory cells, abundant healthy granulation tissue, significant collagen laying, marked vascular proliferation
After healing	Marked collagen laying and fibrosis	Healthy scar tissue

DISCUSSION

Infection has been one of the major problems in process of wound healing and to manage it, application of appropriate cleansing (debridement) method and selection of suitable dressing material is needed.

In Ayurveda, Sushruta told various drugs and preparations for the management of infected wound. Out of all these drugs some have wound debridement/wound cleansing properties and

some other has wound healing properties. It is nearly not possible to provide complete management by using single drug. So there is a need to use a polyherbal preparation for the management of infective wound, which have both wound cleansing and wound healing properties.

Compound Ayurvedic drug is Kashaya(astringent) rasa dominant drug and according to Aachrya Sushruta and Charak kashaya rasa has not only wound debridement/wound cleansing properties but it also has anti-inflammatory property, it also reduces pain and discharge through wound.[15] Under the Nyagrodhadi gana all the four drugs of Compound Ayurvedic drug is mentioned in Sushruta Samhita as a local applicant for the management of infective wound.[16]

Impregnated dressings is the type of dressing material we have chosen for the study. This dressing material consists of a Biodegradable polymer as a substrate impregnated with compound Ayurvedic drug. This dressing material is easy to apply, cost effective, comfortable, allows non-traumatic removal, and low-adherent.[17] Several authors have found that impregnated dressings are more effective than other non-adherent dressings.

Study showed that pain was significantly reduced in Group II where Wound healing dermal patch was used,in this 100% patients were relieved than Group I where 83% patients were relieved in mild to moderate infective wound (Figure1).

The variation in the intensity of pain differs in subjects depending upon site of the wound and tissue involved, type of the wound and wound dressing.[18] Pain is significantely reduced due to anti-inflammatory and analgesic properties of the ingredients of compound Ayurvedic drug.

Study showed that Discharge was significantly reduced in Wound healing dermal patch treated Group II where 100% patients were relieved than Group I where 72% patients were relieved in mild to moderate infective wound(Figure2). Discharge was significantly reduced in mild to moderate infective wound in group II.

Wounds when become chronic usually are associated with infection. The debris from the wound is constantly shed off in the form of slough or discharge. Even in the initial stages of the wounds (i.e. during the inflammatory phase), wound drainage containing dead cells and debris is shed off which is called as exudates which is nothing but discharge. Decrease in

discharge in Group II, may be due to Astringent nature, wound debridement/wound cleansing properties of trial drug's ingredients.[19]

Study showed that Slough was significantly reduced in Wound healing dermal patch treated group II where 72% patients were relieved and in group I where 77% patients were relieved (almost equal) in mild to moderate infective wound. (Figure3).

Slough was significantly reduced in both groups but as mean difference was more in mild to moderate infective wound, so slough was observed to be more relieved in group II of mild to moderate infective wound. Slough were peel out easily and earlier in trial drug treated group II instead of group-I, it shows the wound cleansing property of trial drug.[20]

Study showed that Surface area was significantly reduced in Wound healing dermal patch treated group II from 36.91±22.11 to 1.03±2.42 more than group I where it reduced from 31.94±18.18 to 0.45±1.67 in mild to moderate infective wound. Surface area were significantly reduced in trial drug treated group II instead of group-I. This proves wound healing property of trial drug (Figure 4).

Study showed that Unit Healing Time was significantly reduced in Wound healing dermal patch treated group II from 0.967±0.102 to 0.220±0.423 and in group I where it reduced from 0.791±0.058 to 0.168±0.324 in mild to moderate infective wound(Figure 5). Study showed that Unit Healing Time was significantly reduced in Wound healing dermal patch treated group II where mean difference was 0.4430±0.404 and in and patients of group I where mean difference 0.6418±.5377 in mild to moderate infective wound. Unit healing time were significantly reduced in trial drug treated group II instead of group-I. Thus it proves wound healing property of trial drug.

Hence, this clinical study clearly reveals that the Wound healing dermal patch (Compound Ayurvedic drug) possess wound healing ,wound debridement/wound cleansing properties. Hence the Compound Ayurvedic drug has anti-inflammatory and analgesic properties, checks excessive exudation and absorbs pus, thus reduces discharge.

So polyherbal preparation, "Compound Ayurvedic drug", used in this study acts effectively as wound healing, for wound debridement and also facilitates the growth of healthy granulation tissue.

In Histological study the trial drug group II gave better healing response than group I, and the difference between group II and group I was significant in mild to moderate infective wound.

CONCLUSION

Topical application of wound healing dermal patch (PLA-CAD) reduces pain, discharge, slough, surface area, and unit healing time of the surrounding tissue substantially in comparison to control group (MEGEHEAL). The wound debridement and wound healing properties of dermal patch is found efficacious. Initially drug acts as a debriding agent, removes slough and necrotic agent from wound and subsequently promotes smooth and uncomplicated healing process. The dressing with wound healing dermal patch provides moist environment to the wound which helps in wound bed preparation resulting in enhancement of the granulation tissue formation and epithelialization. Hence, it can be concluded from the clinical observations that PLA-CAD drugs used for wound management are good wound debriding agents and wound healing agents in comparison to control group (MEGEHEAL).In the results it was noticed that there were statistically significant p values in trial drugs on all these parameters intra-group and inter-group comparison showed non significant p values.

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