

Role of Different Topical Agents in Chronic Nonhealing Lower Limb Ulcers

D Srinivas, B Sharada

Assistant Professor, Department of General Surgery, Mahatma Gandhi Hospital, Warangal, Telangana, India

Abstract

Introduction: Chronic wounds mostly affect people over the age of 60. The incidence is 0.78% of the population and the prevalence ranges from 0.18% to 0.32%. As the population ages, the number of chronic wounds is expected to rise. 4 venous ulcers account for about 70-90% of chronic wounds.

Materials and Methods: This is a prospective, observational study to evaluate the safety and efficacy of RhPDGF-BB gel 0.01%, papain-urea and sodium hyaluronate cream in patients aged between 18 and 75 years with chronic leg ulcers.

Results: They are tabulated in proper format in various tables in manuscript.

Conclusion: Chronic nonhealing ulcers are of major concern to the society and the health-care system in terms of prolonged course of treatment and loss of productivity and work hours. Any alteration in the normal physiological pathway of wound healing leads to formation of a chronic wound, with a protracted course characterized by prolonged inflammatory phase and elevated protease activity resulting in impaired healing.

Key words: Chronic wounds, Diabetic ulcer, Growth factors, Non-healing

INTRODUCTION

A chronic lower limb wound is a wound that does not heal in an orderly set of stages and in a predictable amount of time the way most wounds do.¹ Chronic wounds mostly affect people over the age of 60.² The incidence is 0.78% of the population, and the prevalence ranges from 0.18% to 0.32%.³ As the population ages, the number of chronic wounds is expected to rise.⁴ Venous ulcers account for about 70-90% of chronic wounds.⁵

Chronic nonhealing wounds are a challenge to the patients, as well as to the health-care professional and the health-care system. They significantly impair the quality of life for millions of people. Intensive treatment is required and imparts an enormous burden on society in terms of loss of productivity and man-hours. Therefore, the study of chronic nonhealing wounds is vitally important.

Chronic wounds are a frequently encountered problem that is produced by trauma or pathological insults. Characteristics of chronic wounds include a loss of skin of underlying tissue and do not heal with conventional types of treatment, with a responsible time period.

Any alteration in any of the normal physiological process or any metabolic or pathological attribute of wound or any metabolic or pathological attribute of wound healing can lead to the formation of a chronic wound.

Chronic wounds are characterized by a prolonged inflammatory phase, which ultimately results in elevated protease activity and the subsequent degradation of growth factors and the positive wound healing factors; overall effect is impaired healing.⁶

Since chronic wounds express growth factors necessary for healing in deficient quantity, healing may be fastened by replacing or stimulating those factors and by preventing the excess formation of proteases that break them down.^{7,8}

There are several ways to increase growth factors concentration in chronic wounds like local applications/topical agents of growth factors directly or spread a gel of patient own platelets onto the wound, which then secrete

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Corresponding Author: Dr. D Srinivas, H No: 1-7-1010/3, Road No 1, Santhosh Nagar, Advocates Colony, Hunter Road, Hanamkonda, Warangal 506002, Telangana. E-mail: haritv2002@gmail.com

growth factors such as vascular endothelial growth factors, insulin growth factors-1,2, platelet-derived growth factors (PDGF), transforming growth factors $-\beta$ (TGF- β), and endothelial growth factor (EGF).^{3,8} The most studied growth factors are PDGF fibroblast growth factor, TGF- β , and EGF, FDA has approved the use of gel (PDGF) as an adjuvant therapy in diabetic ulcers.⁹

Early experimental studies have shown the potential of EGF in promoting wound healing. EGF clearly stimulates epidermal repair in animal excisional and thermal injury models and may also stimulates thickness under repair.¹⁰ Nanny, using a pig partial thickness wound model, reported a dose-dependent increase in thickness of granulation tissue epithelialization with EGF.¹¹

Various types of allogeneic skin substitutes including cultured epidermal substitute, cultured dermal substitute, cultured skin substitute, which are composed of keratinocytes and/or fibroblasts as cellular component have been used as biological wound dressings.

Collagen films containing human growth hormone were prepared, and the release of human growth hormone from these films and their effects on wound healing was evaluated.

In this study, the different topical agents in chronic nonhealing lower limb ulcers used are sodium hyaluronate cream, papain-urea debriding ointment, recombinant human PDGF (RhPDGF), and silver nitrate gel.

MATERIALS AND METHODS

Study Design

This is a prospective, observational study to evaluate the safety and efficacy of RhPDGF-BB gel 0.01%, papain-urea and sodium hyaluronate cream inpatients aged between 18 and 75 years with chronic leg ulcers.

Study Centre

Prathima Institute of Medical Sciences, Karimnagar.

Study Duration

The maximum and expected duration of exposure to the study for an individual subject in treatment and follow-ups up to 12 weeks or complete wound closure, whichever is earlier.

Number of Subjects

A number of subjects were 27.

Informed Consent

Informed consent is obtained from the patient with date. Subject information sheets are provided to the patients, which will be available in three local languages.

Criteria for Selection of Patients

Inclusion criteria

- The patient is able to understand and has signed the informed consent form. In the case of compromised mental capacity, approval and signature of a legal guardian are required.
- A diagnosed case of venous insufficiency both by clinical evaluation and any of the supporting diagnostic tests as objective evidence.
- The largest ulcer is no <2 sq.cm and no more than 50 sq.cm.
- Patients are expected to be available for the 12 week study period and are able to adhere to the treatment regimen.
- Patients, male or female patients between 18 and 75 years at the time of consent.
- If the patient is female, she must not be of childbearing potential (e.g, surgically sterilized) or if of childbearing potential, she must have used adequate contraceptive precautions (as confirmed by the investigation) 30 days before screening and baseline visit, or must be negative on pregnancy test and must agree to continue such precautions up to end of study.
- The pregnancy test will be done regularly on these patients if these are outdoor patients.
- Ulcers, which remained, open without healing for more than 2-3 weeks (irrespective of the ambulatory treatment administered).
- Ulcers with purulent discharge and nonviable tissue.

Exclusion criteria

- Life-threatening or serious cardiac failure gastrointestinal, hepatic, renal, endocrine, hematological, or immunologic disorder.
- Uncontrolled hypertension Grade-III.
- Squamous cell carcinoma and basal cell carcinoma of the wound.
- Known case of hypersensitivity to incipient.
- Pregnant women and nursing mothers.
- Past history of autoimmune disease.
- Chronic alcohol abuse (40 ml/day for at least 6 months).
- The patient is receiving or has received within 1 month before first visit any treatment is known to impair wound healing including but not limited to, corticosteroids, immunosuppressive drugs, cytotoxic agents, radiation therapy, and chemotherapy.
- Use of any marketed or investigational or herbal medicine or non-registered drugs for wounds in the past 6 months.
- Clinically relevant abnormal hematology or biochemistry values in the opinion of the investigator.
- Any criteria, which in the opinion of the investigator, suggest that the patient would not be complaint with the study.

Table 1: Age distribution - study of various ulcers

Age (in years)	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
31-40	4	0	7
41-50	5	1	3
51-60	2	4	0
>60	0	1	0

Table 2: Age distribution - control various ulcers

Age (in years)	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
31-40	0	0	3
41-50	2	1	2
51-60	2	0	0
>60	0	0	0

Table 3: Study of various ulcers - RhPDGF - BB

Age (in years)	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
31-40	1	0	2
41-50	2	0	1
51-60	1	1	0
>60	0	1	0

RhPDGF: Recombinant human platelet derived growth factors

Table 4: Study of various ulcers - papain-urea

Age (in years)	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
31-40	1	0	3
41-50	2	1	1
51-60	0	1	0
>60	0	0	0

Table 5: Study of various ulcers - sodium hyaluronate cream

Age (in years)	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
31-40	2	0	2
41-50	1	0	1
51-60	1	2	0
>60	0	0	0

- Treatment with a dressing containing any other growth factors or other biological dressings within 30 days before the screening visit.
- Participation in another clinical study within 30 days before the screening visit or during the study.

Discontinuation criteria

During the study following events must be excluded from the study:

Table 6: Study with topical agents in various ulcers

Topical agent	Number of patients with various ulcers		
	Vascular	Diabetic	Traumatic
RhPDGF-BB	4	2	3
Papain urea	3	2	4
Sodium-hyaluronate cream	4	2	3

RhPDGF: Recombinant human platelet derived growth factors

Table 7: Rate of healing (%) various ulcers with RhPDGF - BB gel 0.01%

Period (in days)	Number of patients with various ulcers		
	Vascular (%)	Diabetic (%)	Traumatic (%)
10	48	9	40
15	78	12	62
30	92	28	88
50	100	41	100
60	0	50	0

RhPDGF: Recombinant human platelet derived growth factors

Table 8: Rate of healing (%) various ulcers with - papain-urea

Period (in days)	Number of patients with various ulcers		
	Vascular (%)	Diabetic (%)	Traumatic (%)
10	52	10	42
15	78	18	66
30	91	38	87
50	100	60	100
60	0	76	0

Table 9: Rate of healing (%) various ulcers with sodium hyaluronate cream

Period (in days)	Number of patients with various ulcers		
	Vascular (%)	Diabetic (%)	Traumatic (%)
10	46	9	40
15	68	13	60
30	86	26	83
50	100	41	100
60	0	50	0

- A request by the patient to be discontinued from the study.
- The patient requires any treatment/therapy that would compromise the evaluation of the test product.
- The investigator feels that it is not in the best interest of the patient to continue the study.
- There is a lack of adherence to the study protocol.
- An adverse event occurs, whether or not treatment related, which precludes continued treatment.
- Any female patient who becomes pregnant during the course of study.
- If compliance (acceptable compliance - 85%) of the patient is found to significantly outside this range at

two consecutive visits, such subjects will be excluded from the efficacy analysis because of noncompliance to treatment.

Ulcer Groups

Ulcers are classified into 3 groups as follows:

Group-I:

- <5 sq.cm ulcer category patients after screening will be measured for ulcer size and patients having ulcer size.
- <5 sq.cm will be included in the group the subjects with no active infection are given RhPDGF, and ulcer with infection are randomly given Papaya - urease and sodium hyaluronidase.

Group-II:

- 5-10 sq.cm ulcer size category patients after screening will be measured for ulcer size and patients having ulcer.

Group-III:

- >10 sq.cm ulcer size category patients after screening will be measured for ulcer size and patients having ulcer size >10 sq.cm will be included in this group.

Screening of Patients

- Informed consent form for enrolment into study.
- Completion of checklist for inclusion, exclusion, and discontinuation criteria.
- Assigning a screening number.
- Recording of medical history, physical examination, and vital signs.
- Any concomitant medication recorded.
- Wound measurement is recorded.
- Wound swab test for estimation of microbial load is taken.
- Screening tests regarding hematology, biochemistry, and urine analysis are done.
- Advice regarding schedule next visit.
- Urine pregnancy test, if applicable.

Initially, the progress of ulcer is observed daily for 2 weeks, and the duration of observation is changed depending on the further progress of the ulcer. Initially, the wound swab test for the estimation of the microbial load is done every 3-4 days, after which the weekly schedule is followed.

Products

- A. RhPDGF-BB gel 0.01% (RhPDGF - BB).
- B. Papain-urea (debriding ointment and spray).
- C. Sodium hyaluronate cream 0.2%.

RESULTS

- The mean age of the patient groups was around 50 years with a range between 31 and 60 years.
- Traumatic ulcers were common in the younger patients, diabetic ulcers in the older age group whereas vascular ulcers were common at all age groups (Tables 1-9).

DISCUSSION

A total of 27 patients were included in this prospective study in Prathima Institute of Medical Sciences, Nagunur, Karimnagar to study about the role of different topical agents in chronic nonhealing lower limb ulcers.

All the patients in the study and control group were followed up for a maximum period of 8 weeks mainly record the rate of healing and the incidence of secondary infection.

The mean age in this study was 50 with a range between 30 and 60 years. Chronic nonhealing ulcers were more common in the 4-6th decades of life. 11 cases (40.74%) were vascular ulcers, 6 cases (22.22%) were chronic diabetic ulcers, and the remaining 10 cases (37.04%). All the patients were distributed equally for better results.

Chronic diabetic ulcers were common after the fourth decade of life, chronic vascular ulcers were more common in all age groups, and chronic traumatic ulcers did not show any age predilection.

There was complete healing of the ulcer in three patients (2 chronic vascular ulcers and 1 chronic traumatic ulcer) treated with RhPDGF-BB gel, Three patients with papain-urea (2 chronic post-traumatic ulcers and 1 vascular ulcer), and sodium hyaluronate cream applied to three patients (1 chronic vascular ulcer and 1 post traumatic ulcer) complete healing over the period of 8 weeks during which the study was conducted.

Chronic wounds may be associated with active infection, such as cellulitis. In addition, an occasional chronic wound may be the nidus for bacteremia and sepsis. In these cases, administer systemic antibiotics. Alternatively, the wound itself may be infected, without systemic effects. Take steps to lower the bacterial count of these wounds, including topical methods to encourage wound healing. Topically applied growth factors are meant to assist the chronic wound with establishing healthy granulation tissue or epidermal cell function for improved healing.

Several growth factors have been studied to this end. Platelet-derived growth factor has been shown to reduce the size of chronic ulcers by up to 70%, as compared to 17% for placebo, probably via acceleration of provisional wound matrix deposition. EGF supplementation was associated with healing of 8 of 9 wounds. Removing dead tissue and thinning the pus in lesions such as ulcers, burns, wounds, and carbuncles.

RhPDGF-BB gel 0.01% is a topically applied growth factor for the healing of the chronic diabetic foot ulcers. RhPDGF-BB gel activates macrophages, fibroblast and growth factors, induces cell proliferation stimulates angiogenesis, and stabilizes newly formed blood vessels. RhPDGF is designed to mimic the naturally occurring PDGF that is present in the body. RhPDGF activates the healing process and helps in complete wound closure.

Papain-urea ointment is a debriding agent. It works by helping the breakdown of dead skin and pus, which helps improve the recovery time of open wounds. Sodium hyaluronate cream correction of cellular dysfunction, restoration of biochemical balance, adequate blood perfusion, control of bacterial load and activates the healing process and helps in complete wound closure.

Although several growth factors have been currently explored as potentially wound healing agents, RhPDGF and TGF- β are the widely used growth factors in healing of various ulcers. Although PDGF is the only FDA approved growth factor.

This study conducted on 27 patients with chronic lower limb ulcers (vascular, traumatic, and diabetic ulcers) observed for a maximum period 12 weeks for any appreciable results. Results of the study suggest that the RhPDGF-BB, papain-urea, and sodium hyaluronate cream agents are increases the percentage of complete healing of ulcers. These type of topical agents are excellent safety and easy to apply.¹²⁻²³

CONCLUSION

Chronic nonhealing ulcers are of major concern to the society and the health-care system in terms of prolonged course of treatment and loss of productivity and work hours. Any alteration in the normal physiological pathway of wound is healing leads to formation of a chronic wound, with a protracted course characterized by prolonged inflammatory phase and elevated protease activity resulting in impaired healing.

Ulcer healing can be poor with up to 50% of venous ulcers turning into nonhealing ulcers. Ulcer recurrence rates

are also common with up to one-third of these patients being treated for a recurrence. Chronic venous ulcers of lower extremities are associated with negative impact on the quality of life of patients, and they also cause a substantial burden on the monetary resources. Prevention strategies, early identification and proper management are of paramount importance in improving the quality of life and reducing health care costs.

With advancing times, many new products were developed in the management of chronic wounds, such as hydrocolloids, calcium alginates, impregnated films, recombinant growth factors, and allogeneic skin substitutes, but the management of chronic wounds still remains an enigma, with a search for a better product that assists through all the phases of wound healing.

In this study RhPDGF, papain-urea and sodium hyaluronate cream as resulted in a faster rate of wound healing and reduced incidence of secondary infection has necessitating fewer dressings and facilitating early return to work.

Although RhPDGF, papain-urea and sodium hyaluronate cream are not more expensive, removing dead tissue and thinning the pus in lesions such as ulcers, burns, wounds, and carbuncles. These are also works by helping the breakdown of dead skin and pus, which helps improve the recovery time of open wounds, in the long run, the need for fewer dressings, reduced secondary infection needing fewer antibiotics, shortened duration of treatment and consequential early return to work prove ultimately to be more economical.

Thus, the overall advantages of the products (RhPDGF, papain-urea, and sodium hyaluronate cream) make this a better alternative in the treatment of chronic nonhealing ulcers.

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