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DRESSING WITH TOPICAL APPLICATION OF RECOMBINANT HUMAN PLATELET –DERIVED GROWTH FACTOR GEL IN THE MANAGEMENT OF ACUTE AND CHRONIC WOUNDS: A PROSPECTIVE STUDY

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ABSTRACT

The purpose of this study was to determine whether the topical application of recombinant human platelet-derived growth factor gel influences healing of acute and chronic wounds. The proforma was designed to include relevant demographic information, history of illness and examination findings. Study was accomplished by allocating the patients with chronic wounds in to two groups with 25 patients each: study group (group1) and a control group (group 2). Patients were randomized to two groups by block randomization using a computer program. Allocation was concealed from patients and observers. A significant acceleration of epithelialization across the wound surface was noted following daily PDGF treatments. The mean \pm SD was used for quantitative variables. Independent samples t-test was applied, to assess the differences in means of quantitative variables between patients and controls. P- value and Confidence intervals were calculated. $P < 0.05$ was considered as statistically significant. Our preliminary study suggests that the topical application of 0.01% recombinant human platelet-derived growth factor gel accelerates healing of acute and chronic wounds.

Keywords: *Acute and Chronic Wound Healing, Platelet Derived Growth Factor, Topical gel Formulation*

INTRODUCTION

Several growth factors have been identified that play a role in wound healing (Meyer-Ingold, 1993; Rothe and Falanga, 1989). Polypeptide growth factors are a class of potent natural biologic mediators which regulate many of the activities of wound healing including cell proliferation, migration, and metabolism. Platelet-derived growth factor (PDGF) and insulin-like growth factor-I (IGF-I) have been shown to regulate DNA and protein synthesis in bone cells in vitro and to interact synergistically to enhance soft tissue wound healing in vivo.

Wound healing is a complex biologic process that involves the integration of inflammation, mitosis, angiogenesis, synthesis, and remodeling of the extracellular matrix. The results of experiments that indicate those growth factors and their receptors regulate key aspects of soft and hard tissue repair. Results of clinical studies are also reviewed that demonstrate that growth factor treatment accelerates healing of normal tissues and promotes healing of impaired wounds. PDGF is a protein with a molecular weight of 30,000 daltons (Pierce *et al.*, 1991) that is normally secreted by platelets, macrophages, endothelial cells, and, under certain conditions, fibroblasts (Ross, 1989). PDGF promotes a variety of activities in fibroblasts, smooth muscle cells, and capillary endothelial cells including cell mitogenesis and migration and synthesis of protein and extracellular matrix components. PDGF also induces cell chemotaxis and activation of inflammatory cells (Ross, 1989). All of these cellular processes are important in wound healing.

Platelet-derived growth factor is a 25-kd dimeric protein that exists in 2 homodimer forms (AA and BB) or the heterodimer form of AB. The BB form is known to stimulate the development of granulation tissue and to facilitate healing of chronic wounds. A prospective randomized trial that evaluated chronic pressure ulcers revealed that topical recombinant human platelet-derived growth factor (rhPDGF-BB) gel significantly reduced wound volume compared with placebo treatment (Pierce *et al.*, 1992). Similarly, a study of epithelialization rates in chronic ulcers showed that 81% of patients who were treated with rhPDGF-BB gel healed compared with 25% of control subjects (Robson *et al.*, 1992). The specific

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physiologic mechanism that is responsible for the effect of rhPDGF-BB gel is unclear but is thought to involve improved fibroblast recruitment, collagen deposition, and neovascularization (Mustoe *et al.*, 1994).

In the last few decades, our understanding of the wound repair process and the role that growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor-3, play in this process has greatly increased, offering the potential for improved treatment of chronic wounds.

In phase II studies, recombinant human PDGF-BB (rhPDGF-BB) was shown to have a positive effect on healing pressure ulcers (Bowen-Pope *et al.*, 1991; Seifert *et al.*, 1989) and lower-extremity ulcers in patients with diabetes (Grotendorst *et al.*, 1985), suggesting that rhPDGFBB may have clinical applications for promoting wound healing.

The purpose of the study was to determine whether the topical application of rhPDGF-BB gel influences healing in acute and chronic wounds.

MATERIALS AND METHODS

This clinical study was conducted as a prospective study in *Srinivas Institute of Medical Science and Research Centre, Mukka, Mangalore, Karnataka*.

The proforma was designed to include relevant demographic information, history of illness and examination findings. a) Inclusion criteria: -Patients with cutaneous ulcer due to traumatic defects, burns, ulcer of venous etiology, decubitus ulcer, diabetic foot. b) Exclusion criteria: -Patients on treatment with immunosuppressors, corticoids, patients with severe peripheral arteriopathy.

Patients suffering from severe malnutrition, malignant cachexia, autoimmune diseases. At the initial examination, patients' age, sex, general health state and comorbidities, age and size of the wounds as well as previous local and systemic treatments were recorded using a standardized questionnaire.

Study was accomplished by allocating the patients with chronic wounds in to two groups with 25 patients each: study group (group1) and a control group (group 2).

Patients were randomized to two groups by block randomization using a computer program. Allocation was concealed from patients and observers.

In group1 wounds were applied with topical gel containing recombinant human platelet derived growth factor and covered with a sterile dressing bandage. Control (group 2) wounds were dressed with paraffin gauze and covered with standard dry dressings. Dressing change was done daily in both the groups. Treatment efficiency was evaluated with respect to the duration in both the groups. The first evaluation was done on day five. Subsequent evaluations were done at two day intervals until 1 month or complete healing. At the beginning and end of the study, we evaluated the condition of the wound by recording the parameters like proportion of slough, granulation and epithelial tissue. Meanwhile eventual adverse effects were also recorded throughout the follow-up period.

RESULTS AND DISCUSSION

Results

Altogether, 50 patients were included in our study; which included 27 males and 23 females. The gender distributions in the 2 groups were almost similar and there were no statistically significant differences between the study and control groups with respect to gender and age (Table 1). The average age for study group was 64 years and group 2 was 60 years.

Table 1: Age and sex distribution of the study and control group

Study group (Group1)		Study group (Group2)
Mean Age	64	60
Male: Female	13:12	14:11

Traumatic defects, burns, ulcer of venous etiology are the most frequent pathologies in our study (Table 2).

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Table 2: Clinical type of ulcer included in our study

Cause proportion		No of subjects	
Group 1		Group 2	
Venous leg ulcer	6	Venous leg ulcer	5
Decubitus ulcer	5	Decubitus ulcer	6
Diabetic ulcer	4	Diabetic ulcer	4
Burn	5	Burn	5
traumatic wound	3	traumatic wound	2
Others	2	Others	3

The majority of the patients had chronic wounds, which were six months old on an average. The general health was assessed as very good in 20 patients and age-appropriate in 20 patients. 10 patients had a reduced physical state due to comorbidities.

Table 3: Wound condition at the end of study

Wound Features	Group 1 (Wound area in %)
Epithelialization	20%
Granulation tissue	95%
Slough	10%

At the end of 1 month of treatment, slough fell from 60 to 10% in group1. At the same time, the area covered with granulation and epithelial tissue markedly increased drastically in group 1 compared to group 2. The wound size (length x width) fell significantly i.e. from 4.5x3 cm to 3 x 2.5 cm in group 1. Four wounds were completely re-epithelialised at the end of the study. The number of patients reporting wound pain decreased markedly in the course of the five dressing changes compared to control group. A significant acceleration of epithelialization across the wound surface was noted following daily PDGF treatments. Apart from mild discomfort and itching around the wound site in 2 cases, no other significant adverse effects were recorded in study group. Mean & SD were calculated for age and extent of decrease in wound size for 2 groups separately. "Statistical analysis was performed using the SPSS computer package version 20.0. The mean \pm SD was used for quantitative variables. Independent samples t-test was applied, to assess the differences in means of quantitative variables between patients and controls. P-value and Confidence intervals were calculated. P<0.05 was considered as statistically significant.

Discussion

As a fundamental response to tissue injury, wound healing is a normal complex process including four general phases of hemostasis, inflammation, cell proliferation, extracellular matrix production, and remodeling, which usually in each phase occurs consequently in a regulated manner (Gosain and DiPietro, 2004; Mathieu *et al.*, 2006). If the precisely coordinated interplay of inflammatory cytokines, mitogenic growth factors, extracellular components and enzymes such as proteases is disturbed, stagnation of the repair process can occur, resulting in a chronic wound (Scheithauer and Riechelmann, 2003). Chronic wounds are of various origins and have different aetiologies. Vascular causes such as venous insufficiency, arterial occlusive disease, diabetic angiopathy and neuropathy are the most common systemic disorders. At the local level, infections, and the presence of a foreign body in the wound can delay wound healing. In addition, prevailing systemic diseases include malnutrition; malignant cachexia can also hamper wound healing (Izadi and Ganchi, 2005). Taking a systematic and disease-specific diagnosis of these local and systemic factors is a prerequisite for successful wound treatment (Grey *et al.*, 2006). Because of the complex pathophysiology of a chronic wound, therapy should not be directed only toward isolated local factors. Rather, a more holistical approach to treatment should be taken (Schultz *et al.*, 2003). Parameters like size and location of the wound, the degree of exudation, presence of slough, necrosis, and possible signs of infection as well as the healing phase of a wound at any given time of the wound state influence the choice of the appropriate wound dressing (Gillitzer, 2002).

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It has been reported that simian sarcoma virus can transform various PDGF-responsive cell types, including human fibroblasts and bovine smooth muscle cells, allowing these cells to grow in soft agar and in focus formation in monolayer (Ross *et al.*, 1986). The transformations induced by the simian sarcoma virus are thought to be mediated through a PDGF-like molecule, and there is a theoretic possibility that PDGF may lead to transformations itself. Some transformed cells produce PDGF that can bind to receptors on their own surface, inducing tumor expansion, whereas other cells do not have PDGF receptors but secrete PDGF that binds to receptors on connective cells in the tumor environment. Thus PDGF may be involved in tumor proliferation and inducing responses in the tissue environment adjacent to tumors (Ross, 1989). However, there is no evidence that PDGF is capable of transforming cells when added exogenously (Stiles, 1983). Moreover, the ability of rhPDGF-BB to affect tumor growth may be minimized by the poor absorption into the systemic circulation after topical application. There are few reports in the literature of the use of PDGF to stimulate healing of chronic ulcers. However, several authors have investigated a preparation obtained from isolated platelets, known as platelet-derived wound-healing formula (PDWHF), in this context. PDWHF contains a mixture of growth factors, including PDGF, transforming growth factor- β , EGF, and platelet-derived angiogenesis factor. PDWHF is not the same as the recombinant rhPDGF-BB used in this study and, therefore, the results cannot be extrapolated to currently marketed PDWItF products. Knighton *et al.*, (1990) were the first to report initiation of wound healing after once daily administration of PDVWHF to a variety of different wounds of the lower extremity including diabetic neurotrophic ulcers (Knighton *et al.*, 1986; Knighton *et al.*, 1990). Similar success was reported by Atri *et al.*, (1990) who treated a variety of lower extremity wounds with an autologous preparation of PDWHF. Krupski *et al.*, (1991) however, found a homologous preparation of PDWHF to provide no additional benefit over standard therapy in the treatment of lower extremity ulcers. There are four published studies of use of recombinant growth factors to treat chronic wounds in humans. Brown *et al.*, (1991) published an uncontrolled study in various types of chronic wounds and concluded that topically applied rhEGF may be beneficial to healing. Falanga *et al.*, (1992) published a study that described the use of rhEGF in a single center, double-blind, placebo-controlled study to treat 44 patients with chronic venous ulceration of the lower extremity. Although numeric trends were demonstrated favoring the recombinant product, statistical significance was not achieved. A study by Robson *et al.*, has demonstrated the effectiveness of recombinant rhPDGF-BB on the healing of chronic pressure ulcers. Although Robson *et al.*, concluded that rhPDGF-BB was superior to placebo in their study, the results were based on a 28-day model in which the ulcers were not followed up to complete closure. Finally, in a study by Mustoe *et al.*, (1994) it was shown that rhPDGF-BB was effective in reducing the size of chronic, full-thickness pressure ulcers compared with placebo. Ulcers were followed up for only 29 days and, therefore; an effect of rhPDGF-BB on complete wound closure was not demonstrated. Further studies are needed to assess the efficacy and safety of rhPDGF-BB in other types of nonhealing wounds and to address the cost-effectiveness compared with standard care. Further work needs to be performed to characterize this subgroup.

Conclusion

In this study, the effect of a single growth factor, rhPDGF-BB, was evaluated in promoting wound healing in patients with chronic ulcers of the lower extremities. Although several growth factors have been or are currently being explored as potential wound healing agents, PDGF is the first and only growth factor to date to demonstrate a statistically significant effect in our clinical trial. These studies have also demonstrated the clinical efficacy of rhPDGF-BB in the treatment of pressure ulcers; both Robson *et al.*, (1992) and Mustoe *et al.*, (1994) have shown that treatment with rhPDGF-BB for 4 weeks reduces the size of chronic pressure ulcers. *Once-daily topical application of rhPDGF-BB is safe and effective in stimulating the healing of chronic, full-thickness, lower-extremity diabetic neurotrophic ulcers.* Topical rhPDGF-BB gel is known to stimulate the development of granulation tissue and to facilitate the healing of chronic wounds. PDGF gel 100 ug/g, in conjunction with good wound care, significantly increased the incidence of complete wound closure and significantly reduced the time to complete closure of acute and chronic ulcers.

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REFERENCES

- Bowen-Pope DF, Van Koppen A and Schattelman G (1991).** Is PDGF really important? testing the hypothesis. *Trends in Genetics* **7** 413-8.
- Brown GL, Curtsinger L and Jurkiewicz MJ et al., (1991).** Stimulation of healing of chronic wounds by epidermal growth factor. *Plastic and Reconstructive Surgery* **88** 189-96.
- Falanga V, Eaglstein WH and Bucalo B et al., (1992).** Topical use of recombinant epidermal growth factor (h-EGF) in venous ulcers. *Journal of Dermatologic Surgery and Oncology* **18** 604-6.
- Gillitzer R (2002).** Modern wound management. *Der Hautarzt* **53** 130-47.
- Gosain A and DiPietro LA (2004).** Aging and wound healing. *World Journal of Surgery* **28**(3) 321-326.
- Grey JE, Enoch S and Harding KG (2006).** Wound assessment. *British Medical Journal* **332** 285- 88.
- Grotendorst GR, Martin GR and Pencev D et al., (1985).** Stimulation of granulation tissue formation by platelet-derived growth factor in normal and diabetic rats. *Journal of Clinical Investigation* **76** 2323-9.
- Izadi K and Ganchi P (2005).** Chronic wounds. *Clinics in Plastic Surgery* **32** 209-22.
- Knighton DR, Ciresi K and Fiegel VD et al., (1990).** Stimulation of repair of chronic nonhealing, cutaneous ulcers using platelet-derived wound healing formula. *Surgery, Gynecology, and Obstetrics* **170** 56-60.
- Atri SC, Misra J and Bisht D et al., (1990).** Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. *Surgery* **108** 508-12.
- Knighton DR, Ciresi KF and Fiegel VD et al., (1986).** Classification and treatment of chronic nonhealing wounds: successful treatment with autologous platelet-derived wound healing factors (PDWHF). *Annals of Surgery* **204** 322-30.
- Krupski WC, Reilly LM and Perez S et al., (1991).** A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic nonhealing wounds: a preliminary report. *Journal of Vascular Surgery* **14** 526-36.
- Meyer-Ingold W (1993).** Wound therapy: growth factors as agents to promote healing. *Trends in Biotechnology* **11** 38702.
- Mustoe TA, Cutler NR and Allman RM et al., (1994).** A phase II study to evaluate recombinant platelet-derived growth factor-BB in the treatment of stage 3 and 4 pressure ulcers. *Archives of Surgery* **129** 213-9.
- Pierce GF, Mustoe TA and Altmann BW et al., (1991).** Role of platelet-derived growth factor in wound healing. *Journal of Cellular Biochemistry* **45** 319-26.
- Pierce PF, Tarpley JE and Yangihara D et al., (1992).** Platelet-derived growth factor (BB homodimer), transforming growth factor- β 1, and basic fibroblast growth factor in dermal wound healing. *American Journal of Pathology* **140** 1375-88.
- Robson MC, Phillips LG and Thomason A et al., (1992).** Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. *Lancet* **339** 23-5.
- Ross R (1989).** Peptide regulatory factors: platelet derived growth factor. *Lancet* **I** 1179-82.
- Ross R, Raines EW and Bowen-Pope DF (1986).** The biology of platelet-derived growth factor. *Cell* **46** 155-9.
- Rothe M and Falanga V (1989).** Growth factors: their biology and promise in dermatologic diseases and tissue repair. *Archives of Dermatology* **125** 1390-8.
- Scheithauer M and Riechelmann H (2003).** Review part I: Basic mechanisms of cutaneous woundhealing. *Laryngo-Rhino-Otologie* **82** 31-35.
- Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, Stacey MC, Teot L and Vanscheidt W (2003).** Wound bed preparation: a systematic approach to wound management. *Wound Repair and Regeneration* **11** 1-28.
- Seifert RA, Hart CE and Phillips PE et al., (1989).** Two different subunits associate to create isoform-specific platelet-derived growth factor receptors. *Journal of Biological Chemistry* **264** 8771-8.
- Stiles CD (1983).** The molecular biology of platelet-derived growth factor. *Cell* **33** 653-5