ORIGINAL ARTICLE

The Role of the Autologous Platelet-Derived Growth Factor in the Management of Decubitus Ulcer

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☐ **Abstract**

Background/Objective-**Decubitus ulcer is an important medico-surgical problem. Medical therapies mostly lead to failure and many patients with decubitus ulcer will ultimately need reconstructive surgery after long morbidity. The aim of our study was to evaluate the effectiveness of autologous platelet-derived growth factor in the healing of these ulcers when compared to conventional therapies.**

Methods-**This study was a randomized control-designed therapeutic clinical trial. Fifteen patients with twenty decubitus ulcers were randomly assigned to treatment and control groups. Eleven wounds were randomized to treatment groups and received general wound care, dressing and PDGF, and nine were subjected to controlled wound care with the same general management and dressing for two weeks. Ulcer parameters were recorded on the first day and then every three days for two weeks. These parameters were compared in the two groups and data-analyzed by student t-test, Kolmogorov-Smirnov goodness of fit test (K-S), Fisher exact test and analysis of variance (ANOVA). P values less than 0.05 were considered statistically significant.**

Results-**In the treatment group, four patients had complete healing and in others there was reduction in the size of the ulcer. The reduction in the wound area among treatment and control groups was 3.90±2.42 and -1.44±2.24 cm^2 respectively (p=0.001). Reduction in the wound depth in the treatment group compared to the control group was 3.45±2.54 and −2.22±3.76 mm respectively (p=0.001). A seventy percent reduction in the wound area in the treatment group compared to the same change in the control group was 70.80±29.81% and 29.53±49.29% respectively (p=0.001), and a seventy percent reduction in wound depth in the treatment group compared to this change in control group was 70.83±30.56% and −47.68±72.68% (p=0.001).**

Conclusion-**We conclude that topically applied autologous platelet-derived growth factor better promotes wound healing in patients with decubitus ulcers compared to those who receive conventional therapy, and renal failure and sepsis do not suppress the wound healing process in treated patients.**

☐ **Keywords** · Decubitus ulcer, treatment · platelet

Introduction

Decubitus ulcer is one of the dreaded problems in patients confined to bed for a longer periods of time. Most of these patients have underlying medico-surgical problems, making management both difficult and expensive.[1] It has been found that about 5-8% of patients admitted to a hospital in London develop decubitus ulcer. Its frequency is as high as 60% in patients with underlying orthopedic disease. In one third of cases these ulcers are multiple and in elderly patients this occurs in fifty percent of cases.[2] Risk factors for decubitus ulcers are immobility, longstanding pressure applied to a part of the body,[3] increased local temperature,[4] drugs,[2] underlying neurologic and cardio-vascular diseases,[5] nutritional status, increased age[6,7] and decreased fibronectin as an agent that promotes vascularization and epithelialization in ulcers.[8] Ischemic damage to capillary membrane, increased capillary permeability, edema and cellular infiltrate constitute the chain of events that produces cell necrosis and ulcer.[9] Recently, the role of growth factors in the healing process has received considerable attention, especially the experimental use of autologous platelet-derived growth factors in ulcer healing. Polypeptide growth factors are a class of biological material that promote cell proliferation, alone or in concert, with binding to specific cell surface mediators. Molecules classified as growth factors may have additional effects on cell differentiation, motility and matrix synthesis. In vitro demonstrations of these properties have led to the conclusion that such growth factors might play an important role in wound healing.[10,11] In the following study we present a new approach in the treatment of decubitus ulcer, utilizing the circulatory platelets as a source of autologous locally acting growth factors for stimulating the repair and healing of ulcer.

Patients and Methods

Research design and patient selection:

This study is a controlled-design, therapeutic clinical trial with simple random sampling. From all patients with decubitus ulcer who were admitted to the teaching hospitals of Shiraz University of Medical Sciences, eighteen patients with twenty-five decubitus ulcers were entered into the initial study. Three patients died because of their underlying disease, so study continued with fifteen patients and twenty decubitus ulcers. Eleven ulcers were randomized into treatment group (Group I), and nine ulcers in control group (Group II). The inclusion criteria were:

1. Minimal depth and surface area of ulcer, 2 mm and 2 cm^2, respectively.

2. Absence of active infection and necrosis of ulcer.

3. Normal peripheral platelet count (>150.000/ mm^3).

4. Reliability and cooperation of the patient.

5. Sacral and buttock location of the ulcer.

The age and sex of the patients and their underlying diseases had no role in patient selection. The randomization of the patients was on the basis of their hospitalization. The first patient (ulcer) was put in the treatment group (Group I) and the second patient (ulcer) was assigned to control group (Group II). If a patient had two ulcers with similar conditions, they were randomized to the treatment or control groups with lotting. Patients randomized to the treatment group (Group I) received PDGF and dressing, but those who were randomized to the control group (Group II) received only dressing.

Preparation of PDGF:

After informed consent was obtained, 60 ml of blood was drawn into a syringe containing 5 ml of the anticoagulant citrate dextrose. This blood was centrifuged (140 g for 20 minutes at 4° C) to remove red and white blood cells, leaving a platelet-rich plasma. Platelets were removed from the plasma by further centrifugation (800 g for 10 minutes at 4° C), and were then re-suspended in normal saline solution at a concentration of 10^9 platelets/ml. The platelets were then treated with 1 unit/ml thrombin (T-4648; Sigma, St. Louis, Mo.) to create a supernatant that contained the released PDGF. The PDGF-containing suspension was then added to 1 gm of collagen (C-9879; Sigma) to produce a sterile topical salve. Each 10 ml salve, according to the size of ulcer, was used for 5-7 days and then discarded.

Procedure:

At the first visit of each patient a complete history was taken and a physical examination was performed, and the ulcer area and depth and presence of infection and necrosis was noted. Initial paraclinical work-up consisted of hemoglobin, leukocyte and platelet count, BUN and Cr measurement and blood cultures. If an ulcer was infected, it was treated with antibiotics, and when infection was eradicated it was included in the study. At the initial clinical visit, if indicated, the wounds were sharply debrided of all necrotic tissue.

Wound care protocol:

Patients used a once-daily wound dressing protocol described as follows:

Treatment group (PDGF+ dressing):

- ☐ Each ulcer which was free of infection and necrosis was thoroughly washed with isotonic normal saline solution and then a thin layer of PDGF was applied to the ulcer's entire surface. One hour later the ulcer was covered with a paraffin-impregnated gauze and a sterile gauze dressing and left in place for 24 hours. These applications were continued for two weeks, or sooner if complete epithelialization of the wound occurred.

Control group (sterile dressing):

- ☐ Ulcers in this group were washed thoroughly with isotonic saline solution and after one hour they were covered only with paraffin-impregnated and sterile gauze dressing for the next 24 hours. Each patient in the control and treatment group was evaluated every three days for evidence of wound healing.

Standard patient care control:

- ☐ All patients in the treatment and control groups, received supportive traditional wound care throughout the trial, including change in position, use of water-filled pillows and diluted betadine solution to the skin around the ulcer.

Statistical analysis:

For comparison of data between the two groups, student t-test was used. Kolmogorov-Smirnov goodness of fit test (K-S) which was a pre-requisite for t-test was applied. For comparison of mean values of the dependant parameters, such as renal failure and sepsis (evaluation of effect of renal failure and sepsis on wound healing), analysis of variance was applied. Fisher exact test was used to compare the percentage of healing in treatment and control groups.

Results:

Fifteen patients with twenty decubitus ulcers were randomized to treatment and control groups. Initial patient data in each group are shown in Table 1.

Table 1: Characterization of patients enrolled in this study.

Variable	Treatment group (Mean ±SD)	Control group (Mean ±SD)	P value
Age (years)	46.36±22.39	43.55±22.39	0.743
Duration of therapy (days)	12.54±1.75	13.11±1.76	0.483
Wound area (cm^2)	6.0 ±3.09	7.11 ±3.72	0.475
Wound depth (mm)	5.09 ±3.61	4.33 ±1.65	0.510
Platelet count (×1000)	289 ±111.6	252.7±117.3	0.488

As shown, there is no statistically significant change between the age of patients, platelet number, duration of therapy and initial area and depth of ulcers in the two groups.

Wound healing rates were determined and the results are shown in Table 2.

Table 2: Result of Healing

Healing criteria	Treatment group (Mean±SD)	Control group (Mean±SD)	P value
Change in area (cm^2)	3.90±2.42	-1.44±2.24	0.001
Change in depth (mm)	3.54±2.54	-2.22±3.76	0.001
Percent of change in area	70.80±29.81	-29.53±49.29	0.001
Percent of change in depth	70.83±30.56	-47.68±72.68	0.001

At the end of the study, four patients in the treatment group had complete wound healing and a considerable reduction in ulcer size occurred in the rest. In this group, the mean wound area reduction compared to this change in the control group was 3.90±2.42 and –1.44±2.24 cm^2 respectively (p=0.001). The change in ulcer depth in the treatment group compared to the same change in the control group was 3.45±2.54 and –2.22±3.76 mm^3 respectively (p=0.001). A seventy percent reduction in wound area in the treatment group was 70.80±29.81% and the corresponding change in the control group was –29.53±49,29% (p=0.001). The reduction in the depth of ulcer to about seventy percent of initial depth in the treatment group versus the control group was 70.83±30.56% and –47.68±72.68% respectively (p=0.001).

In the control group only one patient showed a reduction in ulcer size and the rest had either no change or an increase in their ulcer size was observed. Four patients in the treatment group had renal failure and wound healing was observed in all of these. Two patients with renal failure having two similar decubitus ulcers and who were treated with simple dressing failed to show ulcer healing. Four patients with sepsis in the treatment group had wound healing, while ulcers in septic patients belonging to the control group did not heal.

Discussion:

Recent advances in the biology of wound healing demonstrate that macrophages and platelets are predominant regulatory cells in the repair process. Platelets are known to release certain factors from alpha granules, four of which have been identified. These are the platelet-derived angiogenesis factor, which causes new capillary formation from the existing micro-vasculature[12]; platelet-derived growth factor (PDGF), which is a potent fibroblast mitogen and chemoattractant[13-15]; platelet-derived epidermal growth factor; and platelet factor 4, considered to be a chemoattractant for neutrophils [14,16]. PDGF was initially isolated from platelets but subsequently found to be synthesized by a variety of normal and malignant cells. It is the product of two genes, PDGF-A and B, which are the source of two distinct PDGF-A and B chains. These two chains can combine to form dimers of PDGF-AA, BB and AB. PDGF-BB is more effective than others. Recently recombinant PDGF-BB (rPDGF-BB) has been successfully used in the management of various ulcers, including decubitus ulcer[17]. In 1986, Knighton et al. showed that the use of autologous platelet factors, by accentuating the formation and epithelialization of granulation tissue, lead to the complete healing of ulcers[18]. In 1990, Atri et al. confirmed that recalcitrant skin ulcers can be stimulated by homologous PDGF to produce reparative cellular response[19]. In this study we used autologous PDGF to promote wound healing in a group of patients with decubitus ulcer. Complete healing occurred in 36% of patients in the treatment group, while in the others a remarkable reduction in the size of ulcers was detected during two weeks of therapy. In the control group, complete healing did not occur in any ulcer, but a reduction in the size of ulcer was detected in 12.5% of patients. So we conclude that topically-applied autologous-PDGF promotes wound healing in patients with decubitus ulcer. Renal failure and sepsis did not adversely influence the wound healing process in treated patients.

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