Comparing the Efficacy of Recombinant Human Platelet Derived Growth Factor (PDGF) Gel Dressing with Conventional Dressing in Emergency wound care in Maxillofacial Surgery

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ABSTRACT

Introduction: The importance of Platelet Derived Growth Factor is well established in wound healing cascade, its ability to stimulate cell migration, cell growth, and other development factors synthesis. We, therefore, performed a retrospective, randomized case-control trial to compare the effectiveness of recombinant human Platelet Derived Growth Factor(rhPDGF) gel dressing with traditional povidone iodine dressing in emergency wound care in maxillofacial surgery. Aim and objective: To evaluate the effectiveness and esthetic outcomes of rhPDGF gel dressing over the conventional dressing and to assess rhPDGF gel dressing as a better alternative to conventional dressing. Materials and methods: 40 subjects with acute lacerated wounds were included into the study and were randomly divided into two groups; Group A (study group) consisted of subjects in whom rhPDGF gel dressing was placed over the wound with collagen. Group B (control group) consisted of subjects in whom conventional povidone iodine dressing was placed over the wound; patients were clinically evaluated every week for a total of 4 weeks. The dressing was changed every 3 days or as required in both the groups following the same standard protocol. Clinical and photographic assessment of the wounds was done at every week’s follow up visit. Results: The subjects in the study group showed superior wound healing and esthetic outcomes as compared to the control group, with a p value <0.001. The overall cosmesis was relatively more acceptable (35%) in the study group as compared to the control group(15%) at 1st week and during 2nd, 3rd, and 4th week, study group showed significantly increased mean overall wound healing score as compared to the control group at p = 0.04, p =0.005 and p = 0.001 respectively. Conclusion: rhPDGF gel provides better wound healing and esthetic outcomes than conventional povidone iodine dressing. KEYWORDS: rhPDGF gel; Povidone Iodine; Wound Dressing; PDGF; Collagen

INTRODUCTION

The treatment and healing of wounds are some of the oldest subjects discussed in the medical literature. Knowledge of the stages involved allows physicians to manipulate wounds and to achieve optimal results in a short period. With recent basic science discoveries of the 1980s and 1990s, physicians can now manipulate the wound with cellular and molecular biological techniques and thus improve outcomes. Normal wound healing follows a predictable pattern that can be divided into overlapping phases defined by cellular populations and biochemical activities: 1. Hemostasis and inflammation; 2. Proliferation, and 3. Maturation and remodeling. All wounds need to progress through this series of cellular and biological events that characterize the phase of healing in order to successfully reestablish tissue injury.

Platelet concentrate has been commonly used in regenerative medicine to facilitate wound healing because it contains numerous growth factors. Due to its chemotactic, mitogenic, angiogenic and stimulating effects contributing to matrix formation and wound bed granulation, PDGF is of particular relevance. PDGF has been shown to be safe, reproducible and effective in mimicking the natural process of soft tissue wound healing as it stimulates the production and secretion of collagenase by fibroblast suggesting a role in the wound healing remodeling phase.

Platelet derived growth factor (PDGF) is an approximately 25KDa, a dimeric protein consisting of 2 disulfide – connected polypeptide chains. It is present in 3 different isofoms, the heterodimer PDGF-AB (consisting of an α and β chains) and 2 homodimers, with 2α or 2β chains (PDGF-AA and PDGF-BB, respectively). PDGF –BB has been shown in preclinical and clinical studies to promote granulation tissue formation at the wound site and to aid in wound healing. Becaplermin (rhPDGF-BB) is produced by inserting the gene for the
PDGF B chain into the *Saccharomyces Cervisiae* yeast using recombinant DNA technology. It has been shown that the biological activity of becaplermin is similar to that of natural PDGF. Becaplermin is formulated for topical administration in a preserved, sodium carboxymethylcellulose-based gel. The aqueous gel formulation has added advantages of providing a moist healing environment.  

Over the past decade, various new dressing materials have been developed, such as alginate, hydrocolloid membrane, and fine mesh gauze, all these materials come with a drawback of permeability to bacteria. On the other hand, biological dressings such as collagen create the most physiological interface between the surface of the wound and the environment and are impervious to bacteria. In terms of ease of application and being normal, non-immunogenic, non-pyrogenic, hypoallergenic, and pain-free, collagen dressing has these added benefits over the traditional dressing. PDGF’s therapeutic effect is seen to be maximum in the early stages of healing and if kept in a moist environment after application over the wounds, the healing effect increases further. It has been found that PDGF stimulates the expression of ERK phosphorylation and c-fos proteins, leading to increased cell proliferation and thus to faster wound healing.

In most of the surgical, orthopedic, medical, oral maxillofacial and dermatological trials, autologous platelet gel (APG) is commonly used to improve tissue healing. PDGF released locally via platelet gel plays a key role. Both types of tissue regeneration cells are susceptible to growth factors. Fibroblasts are highly receptive to the essential growth factor of fibroblasts, growth factor derived from platelets, insulin-like growth factor and epidermal growth factor.

**MATERIALS AND METHODS**

This was a prospective, comparative study involving a total of 40 subjects (7 women and 33 men) having a mean age of 26 years, who reported to the Department of Oral and Maxillofacial Surgery, V.S Dental College and hospital, Bengaluru and KIMS hospital, Bengaluru.

**Inclusion criteria:** Patients with acute lacerated facial wounds reporting to the casualty of KIMS hospital and V.S Dental College and Hospital, Bengaluru.

**Exclusion criteria:**
1. Infected wounds
2. Old sutured and lacerated wounds
3. Pregnant and lactating women
4. Patients on immunosuppressive agents, steroids or any other drugs likely to cause impaired wound healing
5. Patients in sepsis, underlying osteomyelitis
6. Concomitant diseases (connective tissue diseases, diabetes mellitus)
7. Smokers, alcoholics, and patients with a history of habitual drug abuse
8. History of a bleeding disorder or concomitant treatment with anticoagulant drugs
9. History of keloids or hypertrophic scars

**Study design:** Subjects with lacerated wounds following trauma who fulfilled the inclusion criteria were selected, the study design was discussed, written informed consent was obtained, medical history was recorded, vital signs were monitored, and physical examination was done.

The subjects were divided into 2 groups (20 patients in each group): Group A (study group): subjects in whom recombinant human platelet derived growth factor gel dressing was placed over the wound with collagen. A proprietary preparation of rhPDGF-BB gel by the name Plermin [(0.1%) [Dr. Reddy’s Laboratories Ltd.]] was used in the study (n=20). Group B (control group): subjects in whom conventional povidone iodine dressing was placed over the wound. Surgical debridement of the wound with normal saline was done before wound bed preparation to clean the wound bed of gross debris, slough, foreign bodies, and any evidence of infection and necrotic tissue.

Preoperative photographs were taken prior to the initiation of surgical procedures. After the site of the wound was prepared, the area was anesthetized with 2% lignocaine with 1:8000 epinephrine. The wound was sutured to close the tissue defect as much as possible. An appropriate amount of rhPDGF gel was applied locally to the wound surface and the wound was covered with collagen sheet and moist sterile gauze dressing in group A subjects. For group B subjects, an appropriate amount of povidone iodine ointment was applied to the wound and covered with a sterile gauze dressing. All subjects were treated under the same circumstances following standard protocol.

Subjects were clinically evaluated every week for a total of 4 weeks. The dressing was changed every 3 days or as required in both the groups following the same standard protocol. At each follow up visit the dressings were removed and the wounds cleaned with normal saline. Treatment was considered successful if a clean, healthy raw bleeding wound bed was seen with out any slough. For comparison of all patients, photographic documentation was performed at change of dressings during follow up visits.

The results were drawn by using Wound Evaluation Scale. Statistical analyses used was based solely on the population targeted for therapy.

**Statistical methods:** All statistical analyses used was based solely on the population targeted for therapy.

**Statistical analysis:** The sample design [study group (n=20) and control group (n=20)] used was purposive sampling statistical package for social sciences (SPSS) for windows, version 22.0. Released in 2013, Armonk, NY:IBM Corp, was used to perform statistical analysis.

**Descriptive statistics:** Descriptive analysis of all explanatory and outcome parameters was done using...
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Table 1 - WOUND EVALUATION SCALE

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Step off border</td>
<td>0 for yes, 1 for no</td>
</tr>
<tr>
<td>2</td>
<td>Contour irregularity</td>
<td>0 for irregular &amp;/puckered, 1 for smooth</td>
</tr>
<tr>
<td>3</td>
<td>Scar width</td>
<td>0 for greater than 2 mm, 1 for less than or equal to 2 mm</td>
</tr>
<tr>
<td>4</td>
<td>Edge eversion</td>
<td>0 for sinking &amp;/curling, 1 for absent</td>
</tr>
<tr>
<td>5</td>
<td>Inflammation</td>
<td>0 for redness &amp;/discharge, 1 for absent</td>
</tr>
<tr>
<td>6</td>
<td>Overall cosmesis</td>
<td>0 for poor, 1 for acceptable</td>
</tr>
</tbody>
</table>

Through combining scores of the 6 categorical variables, a cumulative cosmetic score was obtained. A score of 6 is considered as optimal, whereas a score of ≤ 5 is considered as suboptimal. Minimum score that could be obtained was 0 and maximum score was 6.

mean and standard deviation for quantitative variables, frequency, and proportions for categorical variables.

Inferential statistics: Independent student t test was used for compare the mean overall wound healing scores between two groups at different time intervals. Repeated measures of ANOVA followed by Bonferroni’s post hoc analysis was used to compare the mean overall wound scores between different time intervals. The level of significance(p value) was set at p < 0.05.

RESULTS

The study subjects consisted of 16 males and 4 females aged 15-45 years and the control group included 17 males and 3 females aged 11-45 years. All the candidates completed the investigation. None of the study subjects missed the follow up visits.

The comparison of mean overall wound healing scores between the 2 groups at different time intervals is shown in Figure 1.

The overall cosmesis was relatively more acceptable (35%) in study group as compared to control group (15%) at 1st post op week, which eventually increased to 70% in 2nd week, 90% in 3rd week and 100% in 4th week in the study group compared to 35% , 75% in 2nd , 3rd and 4th week respectively in control group.

The test results demonstrated a significant increase in mean overall wound healing scores in study group from 1st post op week to 4th week, ranging from 2.20±1.40 to 5.85±0.37, respectively at p= 0.001.

Multiple comparisons showed that 4th week post operative period showed significantly highest overall mean wound healing scores as compared to other weeks at p=0.001, which was followed by 3rd week showing similar significant increase in the mean scores as compared to 1st and 2nd week having significantly higher mean scores as compared to 1st week at p= 0.001.[Figure 2 &3]

The overall cosmesis was relatively more acceptable (35%) in study group as compared to control group(15%) at 1st week, which eventually increased to 70% in 2nd week, 90% in 3rd week and 100% in 4th week in the study group compared to 35% , 75% in 2nd , 3rd and 4th week respectively in control group.

The study results demonstrated that during the first week post operative period, there was no significant difference between 2 groups. During 2nd , 3rd and 4th week, the study group showed significantly increased mean overall wound healing scores as compared to the control group at p= 0.04, p=0.005 and p= 0.001 respectively. [Figure 1]

DISCUSSION

Face being a highly esthetic region; facial wounds have become one of the health care system's most drastic obstacles by putting a huge drain on health care services.9 The complications in wound healing after any operation posed a major challenge to the surgeon, especially in the case of traumatic etiologies. Scar formation is one of the healing process's most undesirable results.10 Compared to a placebo gel, becaplermin gel significantly increased the incidence of complete wound closure by 43% and decreased the time for complete wound closure by 32%.11 Collagen membrane was used in our research together with rhPDGF gel, with the former being used as a gel scaffold thereby strengthening the newly formed matrix

Figure 2- study group

Figure 3- control group
during initial healing phase. These two acting symbiotically, thus improved and accelerated the wound healing process.12

Since the biological activity of rhPDGF-BB is regulated by alpha 2 macroglobulin, brief systemic exposure and rapid protein elimination by normal metabolic routes are observed in grafts. Evidence of clinical trials (605 participants) and industrial use of products containing rhPDGF showed that these drugs are not associated with increased incidences of adverse events, carcinogenicity or tumor development. Due to its ability to promote hemostasis, and to cause mesenchymal cell proliferation and differentiation, collagen dressing has been widely used in medicine and dentistry.13

A few records of topical use of rh PDGF to promote wound healing in patients are available. Robson et al.15 assessed the effect of rhPDGF-BB on chronic pressure ulcer healing in a double blind study including 20 patients and found that the subjects treated for 28 days for chronic pressure ulcers with rhPDGF-BB, had smaller ulcers than placebo treated subjects. Mustoe et al.16 assessed the effect of rhPDGF-BB in a double blind , placebo controlled study of 41 patients with deep pressure ulcers. At the end of 28 days of treatment , the ulcers were reduced in size in patients treated with rhPDGF-BB compared with subjects treated with placebo.

Our study demonstrated statistically significant improvement in the step off border of the wounds, by the end of the 1st week of follow up, both the study and control group showed nearly similar step off border of wound edges( 90% of subjects in study group and 80% in control group). By the end of 4th week of treatment , only 5% of subjects in the study group showed step off border which was significantly less than the control group (40%). Thus, demonstrating regenerative capacity of rhPDGF gel.

Steed et al.17 investigated the efficacy of rhPDGF-BB in treatment of lower extremity diabetic ulcers in 118 patients and found a greater reduction in overall wound size in patients treated with rhPDGF-BB group than in placebo group and after 3 weeks of treatment, the disparity was noticeable and sustained during the remainder of the trial. Our study results showed that a significantly greater number of patients treated with rhPDGF-BB gel demonstrated complete wound closure during the course of 4 weeks study compared with patients treated with placebo and showed a trend towards a greater reduction in wound area than the control group. The scar width of the wound was seen to be reduced early during the course of treatment (2mm) more significantly in study group (45%, 65%, 80%and 90%) as compared to control group(25%, 45%, 70% and 85%) during 1st, 2nd, 3rd and 4th week respectively. Sinking / curling of wound edges got improved by 100% in study group as compared to only 80% improvement in control group.

In our study the subjects in both the groups showed irregular contour of the wound during initial period of treatment phase (75% in both the groups). No significant difference was noted during first 15 days of follow up period. However, during the 4th week, study group showed 100% improvement leading to smooth contour of the wound, while 15% of control group demonstrated irregular wound edge contour. Studies have demonstrated that epithelialization and granulation formation appears earlier in patients treated with Autologous Platelet Gel when compared with conventional dressing.18

PDGF enhances DNA synthesis, induces extracellular matrix production in wound repair, and increases collagen deposition.21 An additional crucial wound healing property of rhPDGF-BB is the promotion of new blood vessels formation via up-regulation of VEGF 19 and stabilization of new capillaries by mural cells.20 It has also found to enhance periodontal bone repair in rats and humans.22-24

The purpose of this study was to compare the efficacy of rhPDGF gel dressing with conventional povidone iodine dressing in emergency wound care. It was hypothesized that rhPDGF gel is more efficacious and will provide better esthetic outcomes and enhanced wound healing when compared to conventional povidone iodine dressing. The results of the study confirmed the hypothesis. The study subjects demonstrated statistically significant improvement in wound healing following the use of rhPDGF gel over the wounds ,thus proving rhPDGF gel as a better alternative to conventional dressing.

Collagen is a biomaterial that facilitates wound healing fibers and granulation tissue in the wound bed, providing a healthy wound healing environment. It not only facilitates angiogenesis but also strengthen the repair mechanisms of the body, these reduce edema and fluid loss from the wound site while acting as mechanical support, along with facilitating the migration of fibroblast into the wound and enhancing the metabolic activity of granulated tissue.3 Various other biological dressings include amniotic membrane and autologous skin graft. Amniotic membrane carries a risk of transmission of infection whereas homograft skin has a disadvantage of an additional wound management.25-29 Hence, we found collagen as a better choice for the study due to its ease of application and aids in bleeding control.30

CONCLUSION

In this study, we assessed the ability of a single growth factor(rhPDGF-BB) to promote wound healing. This comparative, prospective study demonstrated that every third day application of rhPDGF-BB gel is safe and stimulates rapid healing of acute lacerated wounds. Hence this easy to use, economical and all natural treatment is a major addition to facial wound care armamentarium, based on a firm understanding of the natural wound healing cycle.
REFERENCES


