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Original Article

Treatment of non-healing sternum wound after open-heart surgery with allogenic platelet-rich plasma and fibrin glue-preliminary outcomes

Mohammad Abbasi Tashnizi[1], Daryoush Hamidi Alamdari[2], Mohammad Esmail Khayami[3], Hamid Reza Rahimi[4], Aliasghar Moeinipour[1], Ahmad Amouzeshi[1], Alexander M. Seifalian[5]

[1]Department of Cardiac Surgery, Imam Reza Academic Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Stem cell and Regenerative Medicine Research Group, Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Mashhad, Iran [4]Student Research Committee, Department of Modern Sciences & Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.. [5] Research Department of General Surgery, Division of Surgery and Interventional Science, UCL Centre for Nanotechnology & Regenerative Medicine, University College London, Royal Free Hampstead NHS Trust Hospital, London, UK.

Address for correspondence: Prof. Daryoush Hamidi Alamdari, Stem cell and Regenerative Medicine Research Group, Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: Hamidiad@mums.ac.ir

ABSTRACT

Introduction: Non-healing wound in the sternal region after coronary arteries bypass graft surgery is a serious complication. For healing a chronic wound, several novel approaches have been proposed recently such as using bone marrow stem cells, platelets and fibrin glue (PFG); but a non-invasive method is highly desirable in the first approach for treatment. The current study was undertaken to evaluate the effect of the combination of PFG in one treatment. **Materials and Methods:** We report on the treatment of six patients with life-threatening chronic sternum wounds, which caused septicemia with multi-drug resistant pathogens. The ulcers were extensively debrided initially and were measured and photographed at weekly intervals. The combination of PFG was applied topically on the wound after every 2 days. **Results:** The wounds were completely closed in five patients and significantly reduced in size in one. There was no evidence of local or systemic complications and any abnormal tissue formation, keloid or hypertrophic scarring. **Conclusions:** Our study suggests, in the first approach, PFG can be used safely in order to heal a non healing sternum wound following coronary artery bypass surgery.

KEY WORDS

Chronic wounds; fibrin glue; platelet-rich plasma; sternal wound

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INTRODUCTION

Chronic wounds, which is defined as no measurable healing progress (20-40% reduction in the area) after 2-4 weeks of optimal treatment,[1] are associated with increased morbidity and mortality and poses a serious economic burden on the health-care system. It has been estimated that nearly $25 billion are spent annually in the United States to treat

ulcers.[2] Therefore, it is highly desirable to promote the acceleration of wound healing, which would improve patients' quality-of-life and reduce the economic impact on the health-care system.

Underlying confounding factors such as old ages, diabetes mellitus, microcirculation impairment, systemic hypoxia, atherosclerosis and malnutrition causes chronic wound. Several novel approaches have been proposed for treatment of recalcitrant wounds according to the wound healing mechanism.[3] These are the use of stem cells, platelet-derived growth factors, fibrin glue and each of these approaches has been reported to improve healing in chronic wounds.[4]

Deep sternal wound infection (DSWI) is a dangerous complication of cardiac surgery with a frequency rate from 0.2% up to 8% and a mortality rate from 5% up to 50%.[5] Therapeutic options include debridement with early or delayed closure, closed continuous irrigation, negative pressure wound therapy and partial or complete sternectomy with flap reconstruction, but there is still a general lack of a standard treatment protocol.[6]

Considering the high mortality rate, there is an urgent need for developing further treatment procedures; and in the first approach, a non-invasive method is highly desirable.

In this study, we report on the first six patients included in a clinical trial aiming to evaluate the treatment of chronic sternal wounds using a combined application of platelets and fibrin glue (PFG) where conventional treatment methods (surgical debridement, bacterial balance and moisture balance at least for 4 weeks) have failed.

MATERIALS AND METHODS

Six patients with recalcitrant sternal wounds that did not respond to conventional therapy and their life at risk were included. The conventional therapy was surgical debridement, complementary treatment (such as antibiotic therapy, blood glucose level control, administration of zinc sulphate and multivitamins and irrigation of wound with normal saline) and moisture balance (wet-to-moist dressings) at least for 4 weeks.

The study protocol were reviewed and approved by the Human Research Ethics Committee of Mashhad University of Medical Sciences (Mashhad, Iran). Informed consent was obtained from the patient. Inclusion criteria were the presence of a recalcitrant wound, agreement of the patient to comply with the protocol requirements (afterevery 2 day washing the wounds and applying combined application of PFG) also self-care of wounds and strict compliance to all follow-up visits. Exclusion criteria were pregnancy, active or previous (within 8 weeks of the study screening visit) chemotherapy, current participation in another clinical investigation, current candidates for vascular surgery, angioplasty or stenting, patients presenting with the clinical characteristics of cellulitis at the ulcer site, purulence or sinus tracts that could not be removed by debridement of the wound to be treated, malignant wounds, vasculitis or connective tissue disease, bone marrow involvement (lymphoma — leukaemia) patients treated with corticosteroids, lactating mothers and patients with any systemic infection, malnutrition, microcirculation impairment and systemic hypoxia.

During the platelets preparation in the Blood Transfusion Organisation in Mashhad, Iran, some units had to be discarded due to contamination of platelets unit with red blood cells, which cannot be transfused to the patients, but they passed all viral safety tests according to blood transfusion regulation.

From 400 ml peripheral blood, 25 ml platelet-rich plasma (PRP) was prepared from ABO match donor.[4] A total volume of 25 ml of concentrated fibrinogen was prepared from separated plasma by two biochemical method either cryoprecipitate method or ethanol precipitation method,[7] then mixed with PRP (final volume 50 ml: Platelet-fibrinogen rich plasma [PFRP)]. One millilitre of thrombin was prepared from removed plasma by adding 10% calcium gluconate. Viral inactivation was done for PFRP and thrombin (1 h at 62°C) and frozen in-20°C freezer until use, for a maximum of 3 months. Prior to the application of PFRP, the area of necrotic and devitalized wound was debrided surgically until bleeding was recognized macroscopically. This allowed the PFRP to come into contact with viable wound tissue. In time of using PFRP, 50 ml was mixed with 1 ml thrombin and calcium gluconate and PFG placed on the wound. Finally, paraffin gauze pads were placed over the wound and a bolster of rolled gauze pads placed over the paraffin gauze. This dressing was then wrapped with rolled gauze. After 2 days, the entire dressing was removed and the wound irrigated with isotonic sodium chloride solution. The wound was treated as described above, after every

2 days again for the formation of granulation tissue and closure. The patients were followed up regularly for ulcer closure and any other possible complications. Digital camera pictures were taken on day 0 and every three weeks, until healing. Ulcer dimensions (length, width, depth) were measured on day 0. The endpoint of follow-up was the closure of the wound after topically application of PFG. The antibiotic therapy was based on the antibiogram of the wound swabs.

RESULTS

The patients' characteristics, past medical history, wound size and duration of wound are presented in Table 1. After treatment, the wound was completely closed in 5 patients (100% healing) and significantly reduced in 1 patient (50% healing). Mean age 55.35 ± 9.98 years, 71.5% were male.

Mean healing time (100% healing) for five patients were 16 ± 3.1 weeks. There was no evidence of local or systemic complications and any abnormal tissue formation, keloid, or hypertrophic scarring. Pictures of the wounds, before and after treatment of selected patients are presented in Figures 1 following the same numerical order as in Table 1.

DISCUSSION

In this pilot study, six patients with sternal chronic wound, which did not responded to conventional therapy, were treated with a combination allogenic PFG. After treatment, wounds of five patients were completely closed and in one patient, wounds significantly improved. The appearance of ulcer bed was bleeding during dressing changes and ulcer palpation was noted and considered as a positive indicator for wound healing.

In this study, the rational beyond using PRP is the replenishment of the significantly decreased local concentration of bioactive factors. in chronic wound. In platelets, bioactive factors are in the α-granules and the dense granules. The α-granules contain growth factors such as transforming growth factor-β, platelet-derived growth factor, insulin-like growth factor, fibroblast growth

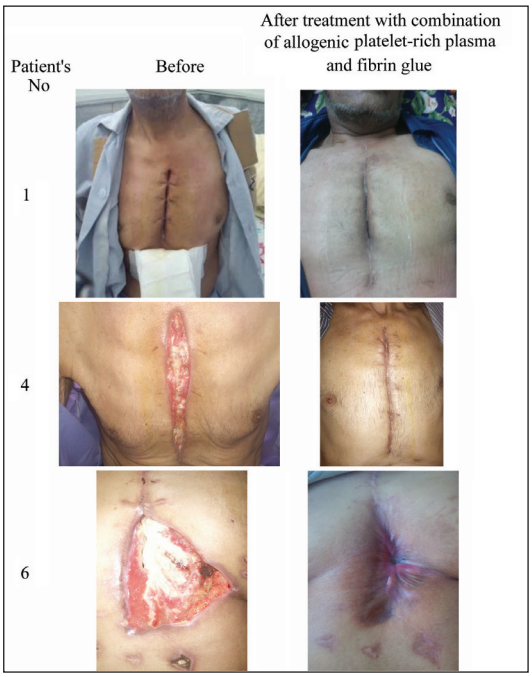

Figure 1: Wounds treatment out come with a combination of allogenic platelet-rich plasma and fibrin glue

Table 1: Patients characteristics, past medical history, ulcer site, categories of wounds and volume (ml) or dimensions (cm) at enrolment, weeks of treatment

Patient no.	Age (years)/gender	Past medical history/ atherosclerosis risk factor	Reason of surgery (CABG, MVR, VSD, etc.)	Length, width, depth (cm) in the sternum	Bacteria isolation from wound	Weeks of treatment and healing situation
1.	62/M	Diabetes mellitus, HLP, HTN	3VD	9×1.5×2	*Staphylococcus aureus*	12 healed
2.	35/F	Congenital heart disease	Congenital VSD	8×3×1	Mix growth	16 improvement >50%
3.	57/M	Diabetes mellitus, HLP	3VD	9×7×1	Gram-negative bacilli	20
4.	60/M	HLP, HTN, heavy smoker	3VD	9×3×1.5	No growth	18
5.	66/M	Diabetes mellitus, HLP	LM, LAD	8×5×1	No growth	16
6.	47/F	Diabetes mellitus and dialysis patient, insulin injection	LM, LAD	5×4×3	*Staphylococcus aureus*	14

M: Male, F: Female, HLP: Hyperlipidaemia, HTN: Hypertension, 3VD: Three vessels disease, 2VD: Two vessels disease, LM: Left main coronary artery, LAD: Left anterior descending, Diabetes mellitus: Non-insulin dependent diabetes mellitus (NIDDM), Heavy smoker: 20 cigarettes/day, MVR: Mitral valve replacement, CABG: Coronary arteries bypass graft, VSD: Ventricular septal defect

factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth factor. The dense granules contain non–growth factors such as serotonin, histamine, dopamine, calcium, and adenosine. These factors play important roles in wound healing.[8,9] In addition, platelets have antimicrobial activity.[10,11]

The rationale behind using fibrin glue that it behaves as a provisional matrix and actively recruits cells to trigger fibrin-mediated responses, such as cell adhesion, migration, proliferation and tubule formation. Fibrin promotes cell growth and vessel formation, which are beneficial during wound repair.[12]

In this study, the patients who needed a long term treatment with platelets, required large volumes of blood and aspiration of such volumes from patients was impossible and therefore, allogenic platelets were replaced. Although, all safety tests were performed for blood bank products, but was on alert on safety concerns. In addition to negative viral tests for platelets, which used for the patients, viral deactivation was performed by heating.

Kachel treated a DWSI by injection of allogenic platelet gel into the wound. Also, few studies in cardiac surgery, applied autologous platelet gel on the wound surface area at the end of the operation as prophylaxis against wound infection rather than as therapy for established DSWI.[8] PFG has been applied for treatment of other chronic wounds In a retrospective cohort study on the effectiveness of autologous platelet releasate in the treatment of diabetic neuropathic foot ulcers, Margolis *et al*. showed that platelet releasate was more likely to be used in more severe wounds and was also more effective in treating these wounds than the standard of care.[13]

In a prospective non-blinded study, Crovetti *et al*. showed the efficacy of once-weekly applications of either autologous or homologous origin platelet gel in healing cutaneous chronic wounds. Nine patients had healed completely and nine had responded partially.[14]

In a prospective, randomized, controlled multicenter trial, Driver *et al*. reported the use of autologous PRP for the treatment of diabetic foot ulcers. The authors found that 68.4 percent of patients in the PRP group and 42.9 percent of patients in the control group had wounds that healed.[15]

In a prospective trial, Jeong *et al*. achieved the complete wound healing in 79 percent of the blood bank platelet concentrate-treated group and 46 percent of the control group ($P < 0.05$). The times required for complete healing were 7.0 ± 1.9 and 9.2 ± 2.2 weeks in the blood bank platelet concentrate-treated and control groups, respectively ($P < 0.05$). No adverse events related to the study treatment occurred.[16]

In a pilot study, Chen *et al*. evaluated the safety and efficacy of combining allogenic single-donor PFG to enhance skin graft take for treating ulcers. He found that the most skin grafts took well. No adverse reactions and recurrence of ulcers was noted during the 3- to -18-month follow-up period.[17]

In a case report, Sell *et al*. treated chronic stage IV pressure ulcers, in three veterans with spinal cord injury, with a sustained release PRP therapy to stimulate wound healing. PRP treatment consistently resulted in the formation of granulation tissue and improved vascularity for each of the three patients treated, while reducing the overall ulcer area and volume.[18]

CONCLUSION

Our results demonstrated the feasibility of our operational model as a non-invasive method as the first approach for treatment chronic sternal wounds. The PFG healed or significantly reduced the wound size in sternal wounds. There was no evidence of local or systemic complications related to the procedure. Based on these results, we are conducting a larger study with the aim of further evaluations of PFG therapy in the treatment of chronic sterna wound.

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